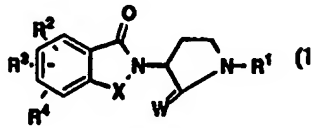
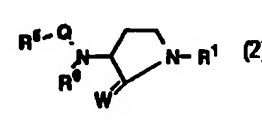




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>C07D 207/12, 209/12, 209/34, 217/24, 401/04, A61K 31/405, 31/47, 31/395</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 97/43257</b> <b>(43) International Publication Date:</b> 20 November 1997 (20.11.97)
<b>(21) International Application Number:</b> PCT/US97/07603 <b>(22) International Filing Date:</b> 6 May 1997 (06.05.97) <b>(30) Priority Data:</b> 60/017,253 10 May 1996 (10.05.96) US <b>(71) Applicant:</b> BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). <b>(72) Inventors:</b> DICKSON, John, K., Jr.; 14 Shelter Rock Road, Eastampton, NJ 08060 (US). ROBL, Jeffrey, A.; 7 Tulip Drive, Newtown, PA 18940 (US). BILLER, Scott, A.; 31 Second Street, Hopewell, NJ 08525 (US). <b>(74) Agents:</b> RODNEY, Burton et al.; Bristol-Myers Squibb Com- pany, P.O. Box 4000, Princeton, NJ 08543-4000 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND METHOD  <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(1)</p> </div> <div style="text-align: center;">  <p>(2)</p> </div> </div> <b>(57) Abstract</b>  Compounds are provided which inhibit microsomal triglyceride transfer protein and thus are useful for lowering serum lipids and treating atherosclerosis and related diseases. The compounds have structure (1) or (2) wherein R <sup>1</sup> to R <sup>6</sup> , Q, W and X are as defined herein.		

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INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER  
PROTEIN AND METHOD

Field of the Invention

5           This invention relates to novel compounds  
which inhibit microsomal triglyceride transfer  
protein, and to methods for decreasing serum  
lipids and treating atherosclerosis employing such  
10           compounds.

Background of the Invention

          The microsomal triglyceride transfer  
protein (MTP) catalyzes the transport of  
triglyceride (TG), cholesteryl ester (CE), and  
15           phosphatidylcholine (PC) between small unilamellar  
vesicles (SUV). Wetterau & Zilversmit, Chem.  
Phys. Lipids 38, 205-22 (1985). When transfer  
rates are expressed as the percent of the donor  
lipid transferred per time, MTP expresses a  
20           distinct preference for neutral lipid transport  
(TG and CE), relative to phospholipid transport.  
The protein from bovine liver has been isolated  
and characterized. Wetterau & Zilversmit, Chem.  
Phys. Lipids 38, 205-22 (1985). Polyacrylamide  
25           gel electrophoresis (PAGE) analysis of the  
purified protein suggests that the transfer  
protein is a complex of two subunits of apparent  
molecular weights 58,000 and 88,000, since a  
single band was present when purified MTP was  
30           electro-phoresed under nondenaturing condition,  
while two bands of apparent molecular weights  
58,000 and 88,000 were identified when  
electrophoresis was performed in the presence of  
sodium dodecyl sulfate (SDS). These two  
35           polypeptides are hereinafter referred to as 58 kDa  
and 88 kDa, respectively, or the 58 kDa and the 88  
kDa component of MTP, respectively, or the low

molecular weight subunit and the high molecular weight subunit of MTP, respectively.

Characterization of the 58,000 molecular weight component of bovine MTP indicates that it is the previously characterized multifunctional protein, protein disulfide isomerase (PDI). Wetterau *et al.*, *J. Biol. Chem.* **265**, 9800-7 (1990). The presence of PDI in the transfer protein is supported by evidence showing that (1) the amino terminal 25 amino acids of the bovine 58,000 kDa component of MTP is identical to that of bovine PDI, and (2) disulfide isomerase activity was expressed by bovine MTP following the dissociation of the 58 kDa - 88 kDa protein complex. In addition, antibodies raised against bovine PDI, a protein which by itself has no TG transfer activity, were able to immunoprecipitate bovine TG transfer activity from a solution containing purified bovine MTP.

PDI normally plays a role in the folding and assembly of newly synthesized disulfide bonded proteins within the lumen of the endoplasmic reticulum. Bulleid & Freedman, *Nature* **335**, 649-51 (1988). It catalyzes the proper pairing of cysteine residues into disulfide bonds, thus catalyzing the proper folding of disulfide bonded proteins. In addition, PDI has been reported to be identical to the beta subunit of human prolyl 4-hydroxylase. Koivu *et al.*, *J. Biol. Chem.* **262**, 6447-9 (1987). The role of PDI in the bovine transfer protein is not clear. It does appear to be an essential component of the transfer protein as dissociation of PDI from the 88 kDa component of bovine MTP by either low concentrations of a denaturant (guanidine HCl), a chaotropic agent (sodium perchlorate), or a nondenaturing detergent (octyl glucoside) results in a loss of transfer



activity. Wetterau et al., Biochemistry 30, 9728-35 (1991). Isolated bovine PDI has no apparent lipid transfer activity, suggesting that either the 88 kDa polypeptide is the transfer protein or  
5 that it confers transfer activity to the protein complex.

The tissue and subcellular distribution of MTP activity in rats has been investigated. Wetterau & Zilversmit, Biochem. Biophys. Acta 875,  
10 610-7 (1986). Lipid transfer activity was found in liver and intestine. Little or no transfer activity was found in plasma, brain, heart, or kidney. Within the liver, MTP was a soluble protein located within the lumen of the microsomal  
15 fraction. Approximately equal concentrations were found in the smooth and rough microsomes.

Abetalipoproteinemia is an autosomal recessive disease characterized by a virtual absence of plasma lipoproteins which contain  
20 apolipoprotein B (apoB). Kane & Havel in The Metabolic Basis of Inherited Disease, Sixth Edition, 1139-64 (1989). Plasma TG levels may be as low as a few mg/dL, and they fail to rise after fat ingestion. Plasma cholesterol levels are  
25 often only 20-45 mg/dL. These abnormalities are the result of a genetic defect in the assembly and/or secretion of very low density lipoproteins (VLDL) in the liver and chylomicrons in the intestine. The molecular basis for this defect  
30 has not been previously determined. In subjects examined, triglyceride, phospholipid, and cholesterol synthesis appear normal. At autopsy, subjects are free of atherosclerosis. Schaefer et al., Clin. Chem. 34, B9-12 (1988). A link between  
35 the apoB gene and abetalipoproteinemia has been excluded in several families. Talmud et al., J.

Clin. Invest. 82, 1803-6 (1988) and Huang et al.,  
Am. J. Hum. Genet. 46, 1141-8 (1990).

Subjects with abetalipoproteinemia are afflicted with numerous maladies. Kane & Havel,  
5 supra. Subjects have fat malabsorption and TG accumulation in their enterocytes and hepatocytes. Due to the absence of TG-rich plasma lipoproteins, there is a defect in the transport of fat-soluble vitamins such as vitamin E. This results in  
10 acanthocytosis of erythrocytes, spinocerebellar ataxia with degeneration of the fasciculus cuneatus and gracilis, peripheral neuropathy, degenerative pigmentary retinopathy, and ceroid myopathy. Treatment of abetalipoproteinemic  
15 subjects includes dietary restriction of fat intake and dietary supplementation with vitamins A, E and K.

In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes.  
20 Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in  
25 the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). The ability of MTP to catalyze the transport of TG between membranes is consistent  
30 with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in the endoplasmic reticulum (ER) membrane to nascent lipoprotein particles within the lumen of the ER.

35 Olofsson and colleagues have studied lipoprotein assembly in HepG2 cells. Bostrom et al., J. Biol. Chem. 263, 4434-42 (1988). Their

results suggest small precursor lipoproteins become larger with time. This would be consistent with the addition or transfer of lipid molecules to nascent lipoproteins as they are assembled.

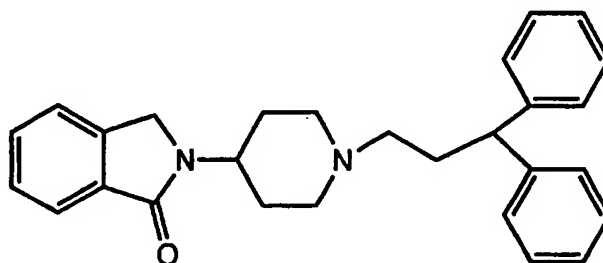
- 5 MTP may play a role in this process. In support of this hypothesis, Howell and Palade, J. Cell Biol. 92, 833-45 (1982), isolated nascent lipoproteins from the hepatic Golgi fraction of rat liver. There was a spectrum of sizes of particles present with varying lipid and protein compositions. Particles of high density lipoprotein (HDL) density, yet containing apoB, were found. Higgins and Hutson, J. Lipid Res. 25, 1295-1305 (1984), reported lipoproteins isolated from Golgi were consistently larger than those from the endoplasmic reticulum, again suggesting the assembly of lipoproteins is a progressive event.

- Recent reports (Science, Vol. 258, page 999, 1992; D. Sharp et. al., Nature, Vol. 365, page 65, 1993) demonstrate that the defect causing abetalipoproteinemia is in the MTP gene, and as a result, the MTP protein. Individuals with abetalipoproteinemia have no MTP activity, as a result of mutations in the MTP gene, some of which have been characterized. These results indicate that MTP is required for the synthesis of apoB containing lipoproteins, such as VLDL, the precursor to LDL. It therefore follows that inhibitors of MTP would inhibit the synthesis of VLDL and LDL, thereby lowering VLDL levels, LDL levels, cholesterol levels, and triglyceride levels in animals and man.

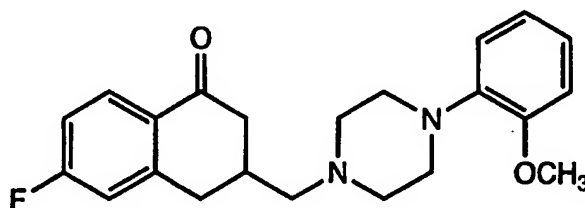
- Canadian Patent Application No. 2,091,102 published March 2, 1994 (corresponding to U.S. application Serial No. 117,362, filed September 3, 1993 (file DC21b)) reports MTP inhibitors which

also block the production of apoB containing lipoproteins in a human hepatic cell line (HepG2 cells). This provides further support for the proposal that an MTP inhibitor would lower apoB

5 containing lipoprotein and lipid levels in vivo. This Canadian patent application discloses a method for identifying the MTP inhibitors



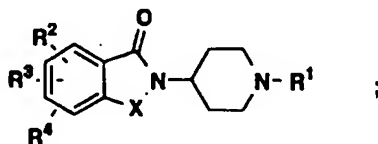
- 10 which has the name 2-[1-(3,3-diphenylpropyl)-4-piperidiny]-2,3-dihydro-3-oxo-1H-isoindole hydrochloride and



- 15 which has the name 1-[3-(6-fluoro-1-tetralanyl)methyl]-4-O-methoxyphenyl piperazine

EP 0643057A1 published March 15, 1995, discloses MTP inhibitors of the structure

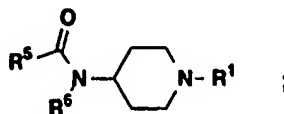
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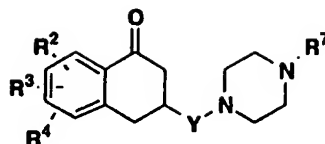
or

II



or

## III



where X is:  $\text{CHR}^8$ ,  $\begin{array}{c} -\text{CH}-\text{CH}- \\ | \quad | \\ \text{R}^9 \quad \text{R}^{10} \end{array}$  or  $\begin{array}{c} -\text{C}=\text{C}- \\ | \quad | \\ \text{R}^9 \quad \text{R}^{10} \end{array}$ ,

5

$\text{R}^8$ ,  $\text{R}^9$  and  $\text{R}^{10}$  are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

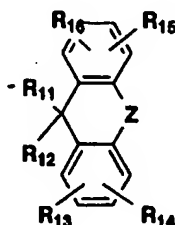
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Y is  $-(\text{CH}_2)_m-$  or  $\begin{array}{c} -\text{C}- \\ || \\ \text{O} \end{array}$

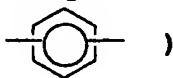
where m is 2 or 3;

$\text{R}^1$  is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl has at least 2 carbons), diarylalkyl, arylalkenyl, diaryl-  
15 alkenyl, arylalkynyl, diarylalkynyl, diarylalkyl-aryl, heteroarylalkyl (wherein alkyl has at least 2 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl has at least 2 carbons); all of the  
20 aforementioned  $\text{R}^1$  groups being optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cyclo-  
25 alkylalkyl, heteroaryl, fluorenyl, heteroaryl-alkyl, hydroxy or oxo; or

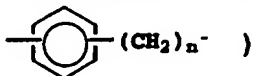
$\text{R}^1$  is a group of the structure



R<sup>11</sup> is a bond, alkylene, alkenylene or alkynylene of up to 6 carbon atoms, arylene (for example



5 or mixed arylene-alkylene (for example



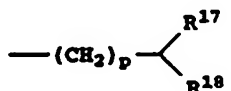
where n is 1 to 6;

R<sup>12</sup> is hydrogen, alkyl, alkenyl, aryl, heteroaryl, haloalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy, heteroarylalkyl or cycloalkylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

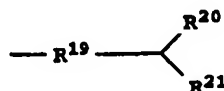
15 R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, and R<sup>16</sup> are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, carboxy, aminocarbonyl, alkylcarbonyloxy, 20 alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or R<sup>1</sup> is



25 wherein p is 1 to 8 and R<sup>17</sup> and R<sup>18</sup> are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of R<sup>17</sup> and R<sup>18</sup> being other than H;

30 or R<sup>1</sup> is



wherein R<sup>19</sup> is aryl or heteroaryl;

R<sup>20</sup> is aryl or heteroaryl;

R<sup>21</sup> is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

5 R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> are independently hydrogen, halo, alkyl, haloalkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

10 R<sup>5</sup> is alkyl of at least 2 carbons, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroaryl-alkyl, cycloalkyl, cycloalkylalkyl, polycyclo-alkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl, polycyclo-  
15 alkenylalkyl, heteroarylcarbonyl, all of the R<sup>5</sup> and R<sup>6</sup> substituents being optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl,  
20 cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkynyl, aryloxy, aryloxyalkyl, aryl-alkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy,  
25 hydroxy, nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, or aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthio-alkyl, alkylcarbonyl, arylcarbonyl, arylamino-  
30 carbonyl, alkoxycarbonyl, aminocarbonyl, alkynyl-aminocarbonyl, alkylaminocarbonyl, alkenylamino-carbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino,  
35 arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino; with the proviso that when R<sup>5</sup> is CH<sub>3</sub>, R<sup>6</sup> is not H; and where R<sup>5</sup> is

phenyl, the phenyl preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl, aryl, aryloxy or arylalkyl;

5  $R^6$  is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkenyl;

$R^7$  is alkyl, aryl or arylalkyl wherein alkyl or the alkyl portion is optionally substituted with oxo; and

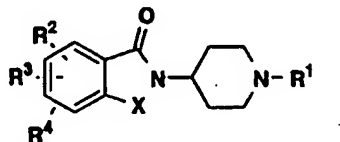
10 including pharmaceutically acceptable salts and anions thereof.

In the formula I compounds, where X is CH<sub>2</sub> and  $R^2$ ,  $R^3$  and  $R^4$  are each H,  $R^1$  will be other than 3,3-diphenylpropyl.

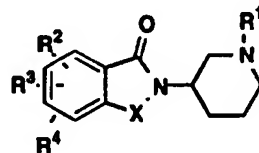
15 In the formula III compounds, where one of  $R^2$ ,  $R^3$  and  $R^4$  is 6-fluoro, and the others are H,  $R^7$  will be other than 4-O-methoxyphenyl.

U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e) discloses compounds of the structure

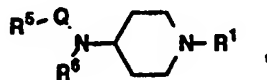
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or

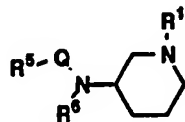


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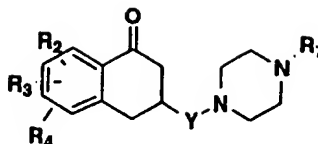
25

or





or



where Q is  $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{--}$  or  $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{S}}}\text{--}$  ;

5

X is:  $\text{CHR}^8$ ,  $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{--}$ ,  $\text{--}\underset{\text{R}^9}{\text{CH}}\text{--}\underset{\text{R}^{10}}{\text{CH}}\text{--}$  or  $\text{--}\underset{\text{R}^9}{\text{C}}=\underset{\text{R}^{10}}{\text{C}}\text{--}$ ;

$\text{R}^8$ ,  $\text{R}^9$  and  $\text{R}^{10}$  are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

10

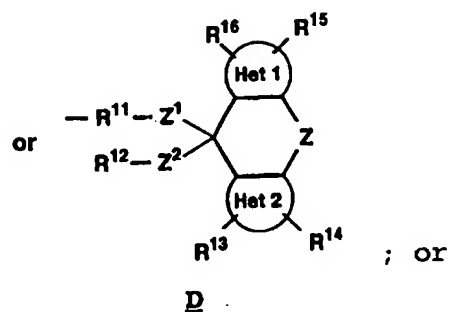
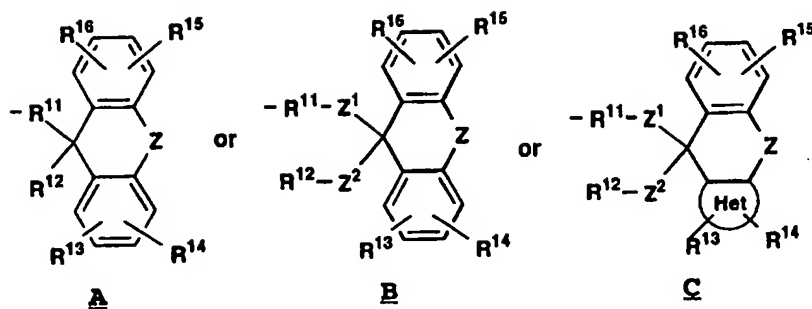
Y is  $\text{--}(\text{CH}_2)_m\text{--}$  or  $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{--}$

wherein m is 2 or 3;

$\text{R}^1$  is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl wherein alkyl has at least 2 carbons, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl wherein alkyl has at least 2 carbons, cycloalkyl, or cycloalkylalkyl wherein alkyl has at least 2 carbons, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

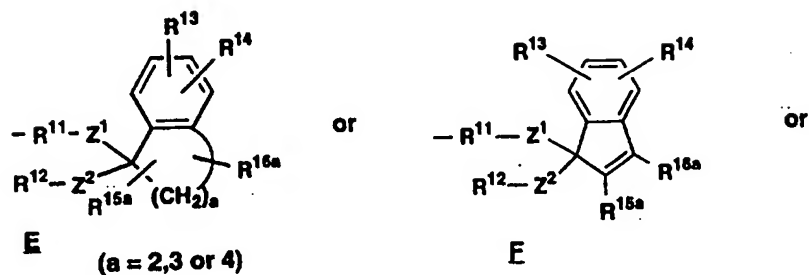
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or  $\text{R}^1$  is a fluorenyl-type group of the structure

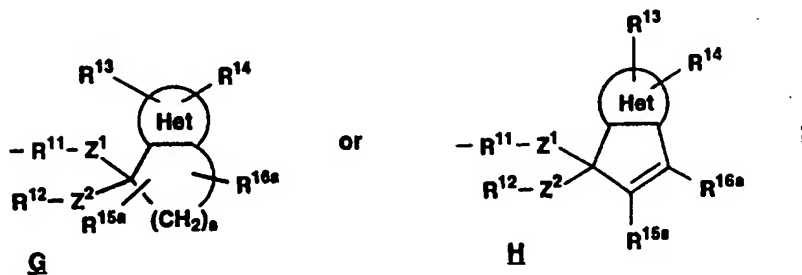


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$R^1$  is an indenyl-type group of the structure

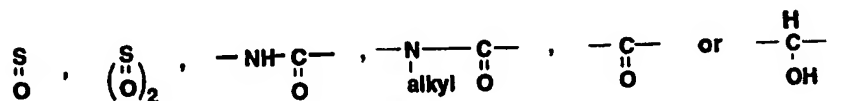


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15

$Z^1$  and  $Z^2$  are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of Z<sup>1</sup> and Z<sup>2</sup> will be other than a bond; R<sup>11</sup> is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; R<sup>12</sup> is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

(1) when R<sup>12</sup> is H, aryloxy, alkoxy or arylalkoxy, then Z<sup>2</sup> is

$$\begin{array}{c} \text{—NH—C—} \\ \parallel \\ \text{O} \end{array}, \begin{array}{c} \text{—N—C—} \\ | \quad \parallel \\ \text{alkyl O} \end{array}, \begin{array}{c} \text{—C—} \\ \parallel \\ \text{O} \end{array}$$

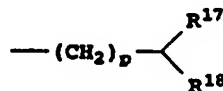
or a bond and

(2) when Z<sup>2</sup> is a bond, R<sup>12</sup> cannot be heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, and R<sup>16</sup> are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cyclo-heteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

R<sup>15a</sup> and R<sup>16a</sup> are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cyclo-heteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

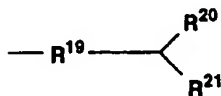
or R<sup>1</sup> is a group of the structure



wherein p is 1 to 8 and R<sup>17</sup> and R<sup>18</sup> are each independently H, alkyl, alkenyl, aryl, arylalkyl,

heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of R<sup>17</sup> and R<sup>18</sup> being other than H;

- 5 or R<sup>1</sup> is a group of the structure

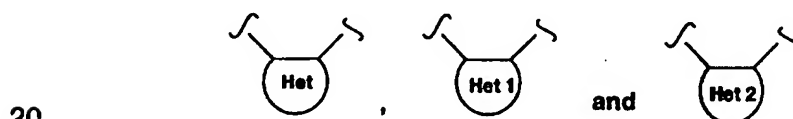


- wherein R<sup>19</sup> is aryl or heteroaryl;  
 R<sup>20</sup> is aryl or heteroaryl;  
 R<sup>21</sup> is H, alkyl, aryl, alkylaryl,  
 10 arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;  
 R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl,  
 15 arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;  
 R<sup>5</sup> is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy,  
 20 heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl,  
 25 heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy,  
 30 haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxy,  
 35 heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino,

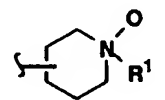
thiol, alkylthio, arylthio, heteroarylthio,  
 arylthioalkyl, alkylcarbonyl, arylcarbonyl,  
 arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl,  
 alkynylaminocarbonyl, alkylaminocarbonyl, alkenyl-  
 5 aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy,  
 alkylcarbonylamino, arylcarbonylamino, arylsul-  
 finyl, arylsulfinylalkyl, arylsulfonyl, alkylsul-  
 fonyl, arylsulfonylamino, heteroarylcarbonylamino,  
 heteroarylsulfinyl, heteroarylthio, heteroaryl-  
 10 sulfonyl, alkylsulfinyl;

$R^6$  is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub>  
 alkenyl; all optionally substituted with 1, 2, 3  
 or 4 groups which may independently be any of the  
 substituents listed in the definition of  $R^5$  set  
 15 out above;

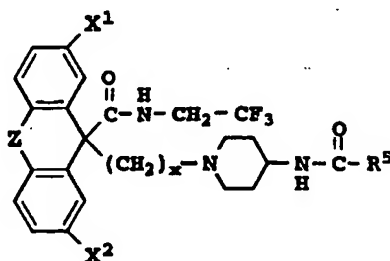
$R^7$  is alkyl, aryl or arylalkyl wherein  
 alkyl by itself or as part of arylalkyl is  
 optionally substituted with oxo  $\left( \begin{smallmatrix} \text{O} \\ || \end{smallmatrix} \right)$ ;



are the same or different and are independently  
 selected from heteroaryl containing 5- or 6-ring  
 members; and

  
 N-oxides thereof; and  
 25 pharmaceutically acceptable salts thereof;  
 with the provisos that where in the first  
 formula X is CH<sub>2</sub>, and  $R^2$ ,  $R^3$  and  $R^4$  are each H,  
 then  $R^1$  will be other than 3,3-diphenylpropyl, and  
 in the fifth formula, where one of  $R^2$ ,  $R^3$  and  $R^4$   
 30 is 6-fluoro, and the others are H,  $R^7$  will be  
 other than 4-(2-methoxyphenyl).

U.S. application Serial No. 548,811 filed January 11, 1996 (file DC21h), discloses compounds having the structure



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including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof, wherein Z is a bond, O or S;

10  $X^1$  and  $X^2$  are independently selected from H or halo;

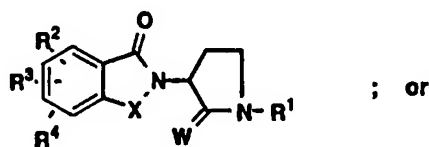
$x$  is an integer from 2 to 6;

15  $R^5$  is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each  $R^5$  group being optionally substituted with 1, 2, 3 or 4 substituents which may be the same or different.

### Summary of the Invention

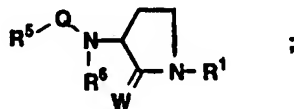
In accordance with the present invention, novel compounds are provided which are inhibitors of MTP and have the structure

I



; or

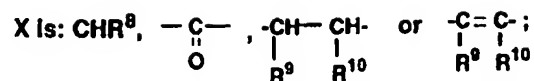
II



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where Q is  $\text{—}\overset{\text{O}}{\parallel}\text{C—}$  or  $\text{—}\overset{\text{O}}{\parallel}\text{S—}$  ;

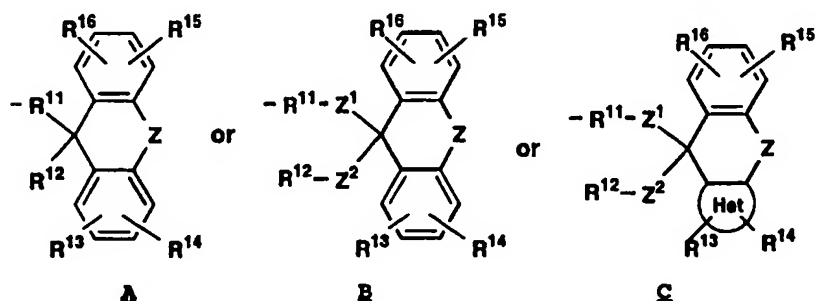
W is H, H or O;

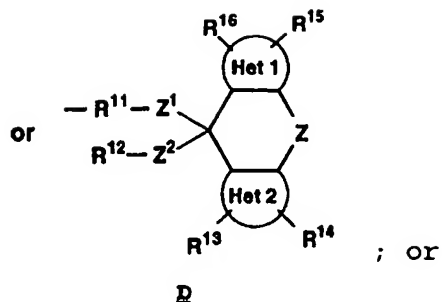


- $R^8$ ,  $R^9$  and  $R^{10}$  are independently hydrogen, alkyl,  
 alkenyl, alkynyl, aryl, arylalkyl, heteroaryl,  
 5 heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;  
 $R^1$  is alkyl, alkenyl, alkynyl, aryl,  
 heteroaryl, arylalkyl (wherein alkyl preferably  
 has at least 2 carbons, more preferably at least 3  
 carbons), diarylalkyl, arylalkenyl, diarylalkenyl,  
 10 arylalkynyl, diarylalkynyl, diarylalkylaryl,  
 heteroarylalkyl (wherein alkyl preferably has at  
 least 2 carbons, more preferably at least 3  
 carbons), cycloalkyl, or cycloalkylalkyl (wherein  
 alkyl preferably has at least 2 carbons, more  
 15 preferably at least 3 carbons); all of the  
 aforementioned  $R^1$  groups being optionally  
 substituted through available carbon atoms with 1,  
 2, 3 or 4 groups selected from halo, haloalkyl,  
 alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl,  
 20 alkylmercapto, arylmercapto, cycloalkyl,  
 cycloalkylalkyl, heteroaryl, fluorenyl,  
 heteroarylalkyl, hydroxy or oxo; or

$R^1$  is a fluorenyl-type group of the  
 structure

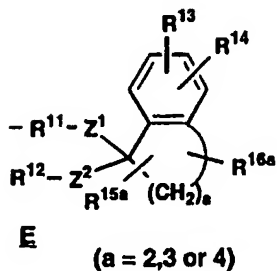
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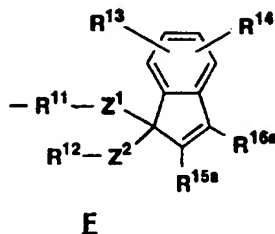


$R^1$  is an indenyl-type group of the structure

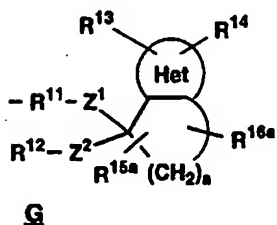
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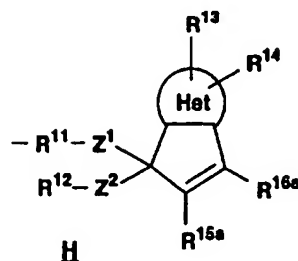
or



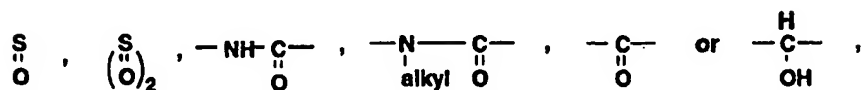
or



or

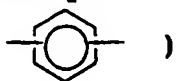


10  $Z^1$  and  $Z^2$  are the same or different and are independently a bond, O, S,



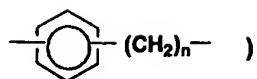
with the proviso that with respect to  $\underline{B}$ , at least one of  $Z^1$  and  $Z^2$  will be other than a bond;

15  $R^{11}$  is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example



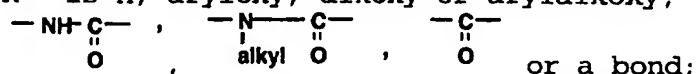
or mixed arylene-alkylene (for example





where n is 1 to 6;

R<sup>12</sup> is hydrogen, alkyl, alkenyl, aryl, halo-alkyl, trihaloalkyl, trihaloalkylalkyl, hetero-  
 5 aryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the provisos that (1) when R<sup>12</sup> is H, aryloxy, alkoxy or arylalkoxy, then Z<sup>2</sup> is



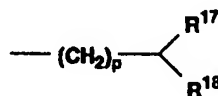
10 and (2) when Z<sup>2</sup> is a bond, R<sup>12</sup> cannot be heteroaryl or heteroarylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

15 R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, and R<sup>16</sup> are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio,  
 20 aminocarbonyl, alkylcarbonyloxy, arylcarbonyl-amino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

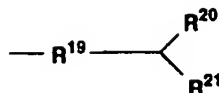
R<sup>15a</sup> and R<sup>16a</sup> are independently any of the R<sup>15</sup> or R<sup>16</sup> groups except hydroxy, nitro, amino or  
 25 thio;

or R<sup>1</sup> is



wherein p is 1 to 8 and R<sup>17</sup> and R<sup>18</sup> are each independently H, alkyl, alkenyl, aryl, arylalkyl,  
 30 heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of R<sup>17</sup> and R<sup>18</sup> being other than H;

or R<sup>1</sup> is



wherein R<sup>19</sup> is aryl or heteroaryl;

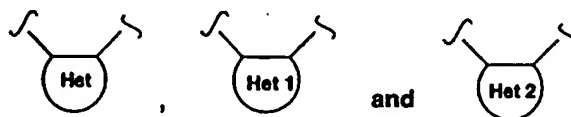
R<sup>20</sup> is aryl or heteroaryl;

R<sup>21</sup> is H, alkyl, aryl, alkylaryl, arylalkyl,  
 5 aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl,  
 heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or  
 cycloalkylalkoxy;

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> are independently hydrogen, halo,  
 alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl,  
 10 alkylmercapto, arylmercapto, cycloalkyl,  
 cycloalkylalkyl, heteroaryl, heteroarylalkyl,  
 hydroxy or haloalkyl;

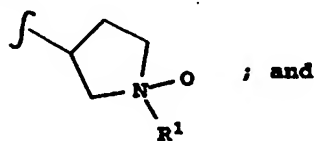
R<sup>5</sup> is alkyl, alkenyl, alkynyl, aryl,  
 alkoxy, aryloxy, arylalkoxy, heteroaryl, aryl-  
 15 alkyl, heteroarylalkyl, cycloalkyl, cyclohetero-  
 alkyl, heteroaryloxy, cycloalkylalkyl, polycyclo-  
 alkyl, polycycloalkylalkyl, cycloalkenyl, cyclo-  
 alkenylalkyl, polycycloalkenyl, polycycloalkenyl-  
 alkyl, heteroarylcarbonyl, amino, alkylamino,  
 20 arylamino, heteroarylamino, cycloalkyloxy, cyclo-  
 alkylamino, all of the R<sup>5</sup> substituents and R<sup>6</sup>  
 substituents (set out hereinafter) being  
 optionally substituted through available carbon  
 atoms with 1, 2, 3 or 4 groups selected from  
 25 hydrogen, halo, alkyl, haloalkyl, alkoxy,  
 haloalkoxy, alkenyl, alkynyl, cycloalkyl,  
 cycloalkylalkyl, cycloheteroalkyl, cyclohetero-  
 alkylalkyl, aryl, heteroaryl, arylalkyl,  
 arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy,  
 30 aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxy,  
 heteroarylalkyl, heteroarylalkenyl, heteroaryloxy,  
 hydroxy, nitro, cyano, amino, substituted amino  
 (wherein the amino includes 1 or 2 substituents  
 which are alkyl, aryl or heteroaryl, or any of the  
 35 other aryl compounds mentioned in the  
 definitions), thiol, alkylthio, arylthio,

- heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylamino-  
 5 carbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonyl- amino, arylsulfinyl, arylsulfinylalkyl, aryl- sulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or  
 10 alkylsulfinyl. Where  $R^5$  is phenyl, aryl, heteroaryl or cycloalkyl; this group preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl (with up to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo groups),  
 15 aryl, aryloxy or arylalkyl;  
 $R^6$  is hydrogen or  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  alkenyl;



- 20 are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

including N-oxides of the formulae I and II compounds, that is

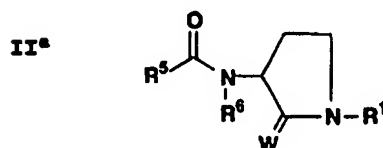
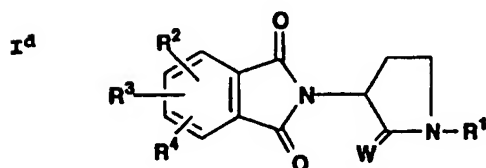
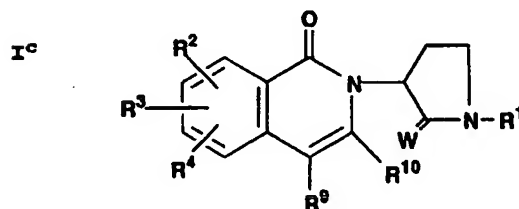
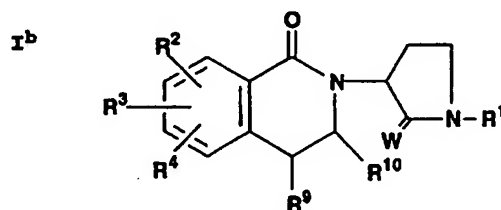
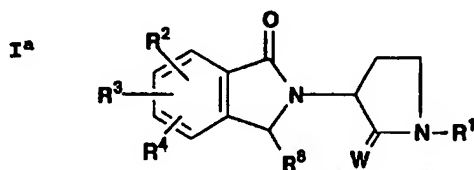


- 25 including pharmaceutically acceptable salts thereof such as alkali metal salts such as lithium sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or  
 30 aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butyl- amine, t-octylamine, dehydroabietylamine, as well as pharmaceutically acceptable anions such as

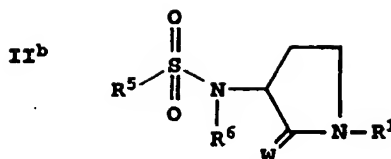
chloride, bromide, iodide, tartrate, acetate, methanesulfonate, maleate, succinate, glutarate, and salts of naturally occurring amino acids such as arginine, lysine, alanine and the like, and  
 5 prodrug esters thereof.

In the formula I compounds, where X is CH<sub>2</sub> and R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are each H, R<sup>1</sup> will preferably be other than 3,3-diphenylpropyl.

Thus, the compounds of formulae I and II of  
 10 the invention encompass compounds of the structure



20



It will be understood that the pyrrolidinyl ring shown in the above formulas depicting compounds of the invention as well as in starting materials and intermediates shown in the Reaction Schemes to follow can be in racemic form or are R- or S-enantiomers.

In addition, in accordance with the present invention, a method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity is provided, wherein a compound of formula I or II as defined hereinbefore is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

Furthermore, in accordance with the present invention, a method is provided for lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, wherein a compound of formula I or II is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

#### Detailed Description of the Invention

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "MTP" refers to a polypeptide or protein complex that (1) if obtained from an organism (e. g., cows, humans, etc.), can be isolated from the microsomal fraction of homogenized tissue; and (2) stimulates the transport of triglycerides, cholesterol esters, or

phospholipids from synthetic phospholipid vesicles, membranes or lipoproteins to synthetic vesicles, membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein [Drayna et al., Nature 327, 632-634 (1987)] which may have similar catalytic properties. However, the MTP molecules of the present invention do not necessarily need to be catalytically active. For example, catalytically inactive MTP or fragments thereof may be useful in raising antibodies to the protein.

The phrase "stabilizing" atherosclerosis as used in the present application refers to slowing down the development of and/or inhibiting the formation of new atherosclerotic lesions.

The phrase "causing the regression of" atherosclerosis as used in the present application refers to reducing and/or eliminating atherosclerotic lesions.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 12 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF<sub>3</sub>, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl,

aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio, as well as any of the other substituents as defined for R<sup>5</sup> and R<sup>6</sup>.

- 5 Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and  
10 tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl,  
15 which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



- 20 any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol  
25 and/or alkylthio, as well as any of the other substituents as defined for R<sup>5</sup> or R<sup>6</sup>.

- The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 5 to 20 carbons,  
30 preferably 6 to 12 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cyclohepta-  
dienyl, which may be optionally substituted as  
35 defined for cycloalkyl.

- The term "polycycloalkyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20 carbons and containing 0 to 3 bridges, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclooctanyl, adamantanyl, [2.2.1]-bicycloheptanyl, [2.2.2]-bicyclooctanyl and the like and may be optionally substituted as defined for cycloalkyl.
- 10 The term "polycycloalkenyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20 carbons and containing 0 to 3 bridges and containing 1 or 2 double bonds, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclooctenyl, [2.2.1]-bicycloheptenyl, [2.2.2]-bicyclooctenyl and the like and may be optionally substituted as defined for cycloalkyl.
- 15 20 The term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to Ar (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxy-alkyl, arylalkoxy, arylthio, arylazo, hetero-arylalkyl, heteroarylalkenyl, heteroarylhetero-aryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or
- 25 30 35



2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonamino-carbonyl, or any of the substituents as defined for the R<sup>5</sup> or R<sup>6</sup> groups set out above.

The term "aralkyl", "aryl-alkyl" or "aryllower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl substituent, such as benzyl or phenethyl, or naphthylpropyl, or an aryl as defined above.

The term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "amino" as employed herein alone or as part of another group may optionally be substituted with one or two substituents such as alkyl and/or aryl.

The term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "acyl" as employed herein by itself or part of another group as defined herein, refers to an organic radical linked to a carbonyl



group, examples of acyl groups include  
5 alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl and the like.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

10 Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 3 to 12 carbons, and more preferably 1  
15 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-  
20 nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cyclo-  
25 alkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R<sup>5</sup> or R<sup>6</sup>.

30 Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2  
35 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butylnyl, 2-butylnyl, 4-pentylnyl, 3-

pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4  
5 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonyl-amino, nitro, cyano, thiol, and/or alkylthio, as  
10 well as any of the other substituents as defined for R<sup>5</sup> or R<sup>6</sup>.

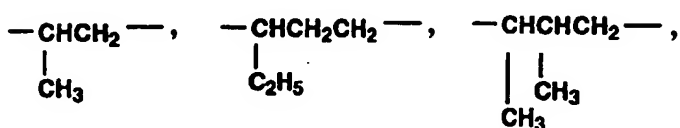
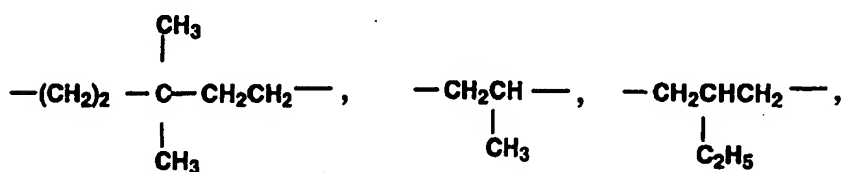
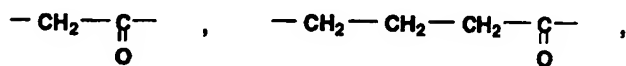
The term "alkylene" as employed herein alone or as part of another group (which also encompasses "alkyl" as part of another group such  
15 as arylalkyl or heteroarylalkyl) refers to alkyl groups as defined above having single bonds for attachment to other groups at two different carbon atoms and may optionally be substituted as defined above for "alkyl". The definition of alkylene  
20 applies to an alkyl group which links one function to another, such as an arylalkyl substituent.

The terms "alkenylene" and "alkynylene" as employed herein alone or as part of another group (which also encompass "alkenyl" or "alkynyl" as  
25 part of another group such as arylalkenyl or arylalkynyl), refer to alkenyl groups as defined above and alkynyl groups as defined above, respectively, having single bonds for attachment at two different carbon atoms.

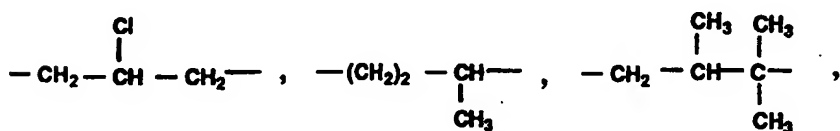
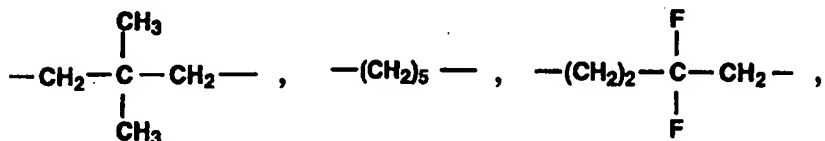
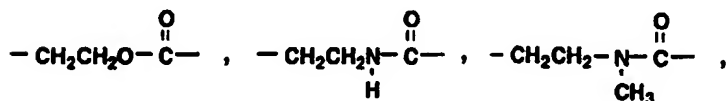
30 Suitable alkylene, alkenylene or alkynylene groups or (CH<sub>2</sub>)<sub>n</sub> or (CH<sub>2</sub>)<sub>p</sub> (which may include alkylene, alkenylene or alkynylene groups) as defined herein, may optionally include 1, 2, or 3 alkyl, alkoxy, aryl, heteroaryl, cycloheteroalkyl,  
35 alkenyl, alkynyl, oxo, aryloxy, hydroxy, halogen substituents as well as any of the substituents defined for R<sup>5</sup> or R<sup>6</sup>, and in addition, may have one

of the carbon atoms in the chain replaced with an oxygen atom, N-H, N-alkyl or N-aryl.

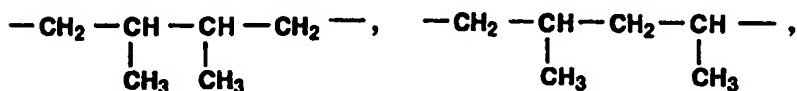
Examples of alkylene, alkenylene, alkynylene,  $(CH_2)_n$  and  $(CH_2)_p$  groups include



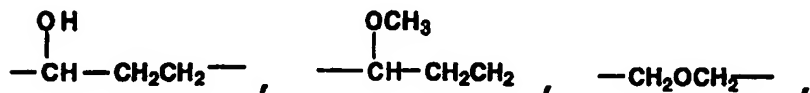
15

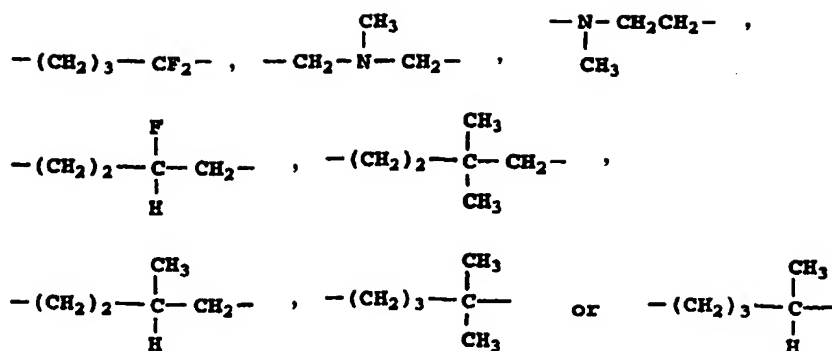


20



25





5

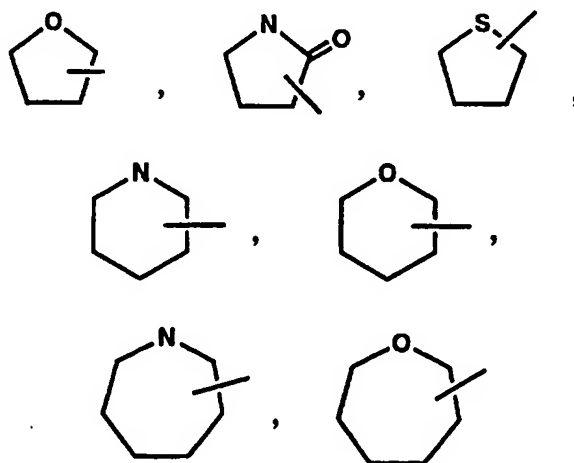
The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF<sub>3</sub>, with chlorine or fluorine being preferred.

10

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

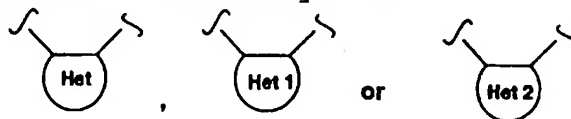
The term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker (CH<sub>2</sub>)<sub>p</sub> (which is defined above), such as

25

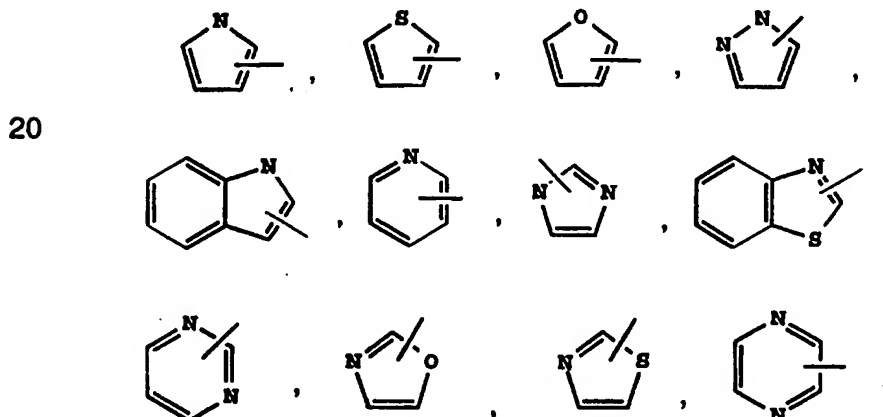


and the like. The above groups may include 1 to 3 substituents such as any of the  $R^1$ ,  $R^5$  or  $R^6$  groups as defined above. In addition, any of the above rings can be fused to 1 or 2 cycloalkyl, aryl, heteroaryl or cycloheteroalkyl rings.

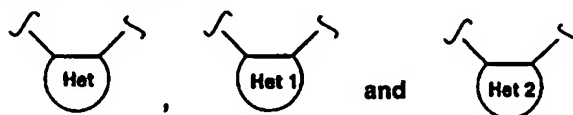
The term "heteroaryl" or



(also referred to as heteroaryl) as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), linked through a carbon atom or a heteroatom, where possible, optionally via the linker  $(CH_2)_p$  (which is defined above), such as

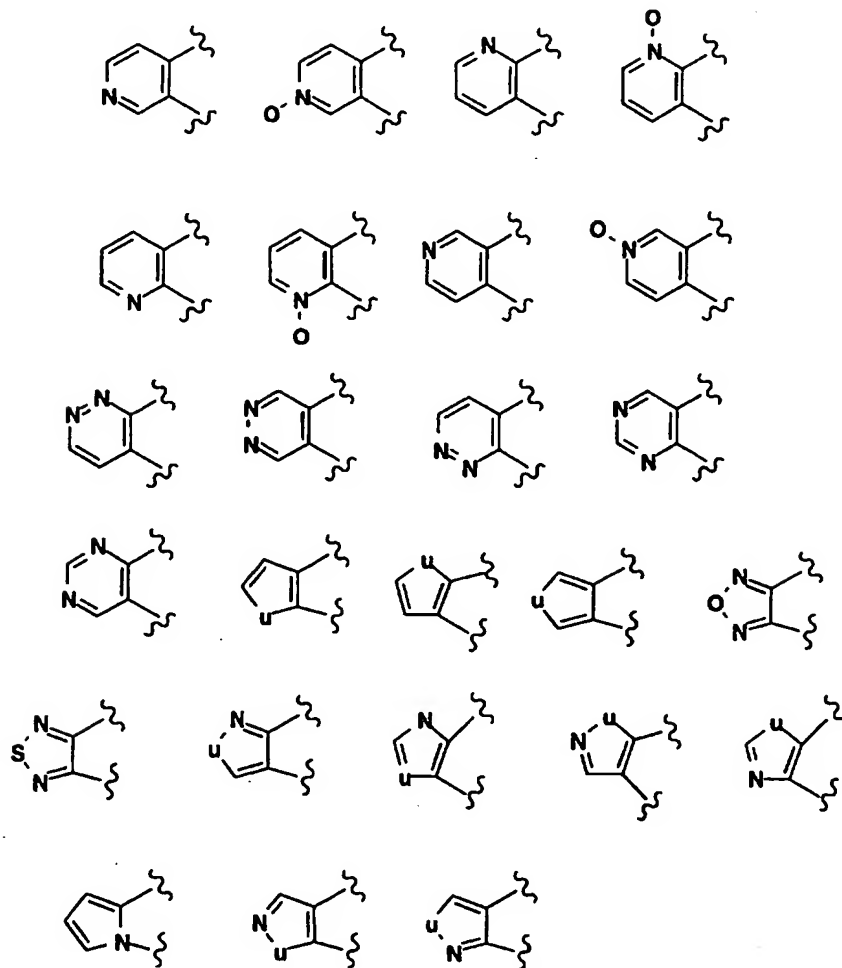


and the like, and includes all possible N-oxide derivatives.



are the same or different as defined hereinbefore and are attached to the central ring of the indenyl or fluorenyl type group at adjacent

positions (that is ortho or 1,2-positions).  
Examples of such groups include



5

wherein u is selected from O, S, and NR<sup>7a</sup>;  
R<sup>7a</sup> is H, lower alkyl, aryl, -C(O)R<sup>7b</sup>, -C(O)OR<sup>7b</sup>;  
R<sup>7b</sup> is alkyl or aryl, and includes all possible N-oxide derivatives.

10

The heteroaryl groups including the above groups may optionally include 1 to 4 substituents such as any of the substituents listed for aryl, or those substituents indicated for R<sup>5</sup> or R<sup>6</sup> groups as defined above. In addition, any of the above

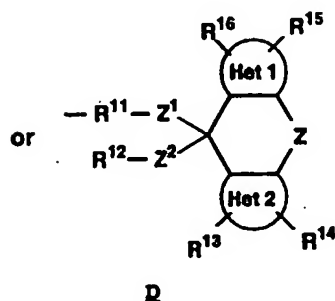
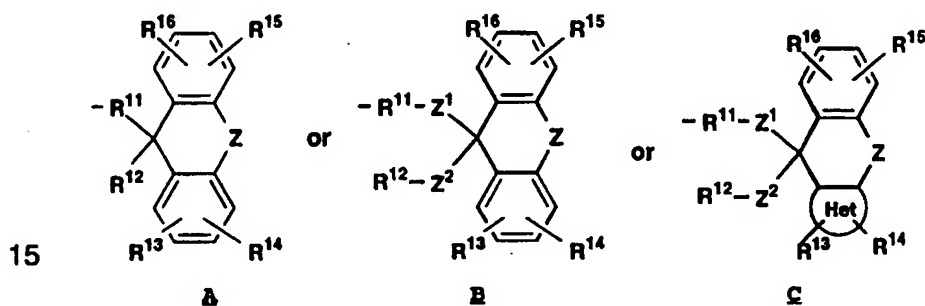
15

rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

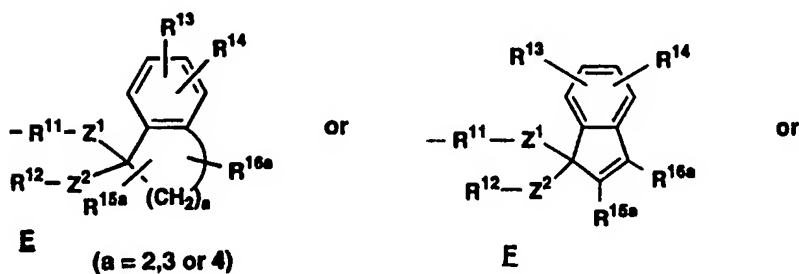
The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a  $(CH_2)_p$  chain.

5 The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a  $-(CH_2)_p-$  chain, alkylene or  
10 alkenylene as defined above.

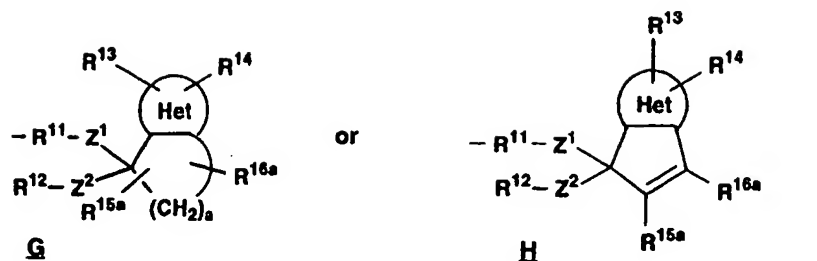
The term "fluorenyl" or "fluorenyl analog" or "fluorenyl-type group" as employed herein refers to a group of the structure:



20 The term "indenyl-type group" as employed herein refers to a group of the structure



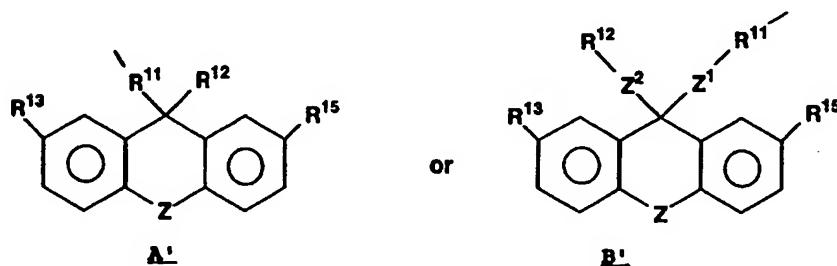




5 Z, Z<sup>1</sup>, Z<sup>2</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>15a</sup> and R<sup>16a</sup> as used in the above groups A through H are as defined hereinbefore.

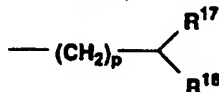
Preferred are compounds of formulae I and II wherein

10 R<sup>1</sup> is arylalkyl, arylalkenyl, heteroaryl-alkyl, heteroarylalkenyl,



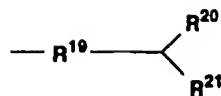
(including where Z<sup>1</sup> is a bond and R<sup>11</sup> is alkylene

15 or alkenylene and Z<sup>2</sup> is  $\text{—NH—C(=O)—S(=O)—}$ ,  $\left(\text{S(=O)}_2\right)$  or  $\text{C(=O)—}$ , and R<sup>12</sup> is C<sub>1</sub>-C<sub>3</sub> alkyl or 1,1,1-trifluoroethyl, R<sup>13</sup> is H or F and R<sup>15</sup> is H or F, and Z is a bond or O; and where R<sup>11</sup> is alkylene or alkenylene or alkylene substituted with oxo, R<sup>12</sup> is alkyl, alkenyl, 20 aralkyl, aralkenyl, Z is O, S or a bond); or



(wherein R<sup>17</sup> and R<sup>18</sup> are each independently alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroaryl-alkyl, cycloalkyl or cycloalkylalkyl); or

25



wherein R<sup>19</sup> is aryl or heteroaryl;

R<sup>20</sup> is aryl or heteroaryl;

R<sup>21</sup> is alkyl, aryl, alkylaryl, arylalkyl  
 5 aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl,  
 heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or  
 cycloalkylalkoxy.

In structure I, it is preferred that R<sup>2</sup>, R<sup>3</sup>  
 and R<sup>4</sup> are each H and X is CH<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>, or CH=CH.

10 In structure II, it is preferred that R<sup>6</sup> is  
 H or CH<sub>3</sub> and R<sup>5</sup> is cycloalkyl, phenyl, aryl or  
 heteroaryl, or cycloalkyl, phenyl, aryl heteroaryl  
 having an ortho hydrophobic substituent which is  
 alkyl, alkoxy, haloalkyl (containing up to five  
 15 halo groups), trifluoromethyl, aryl, aryloxy,  
 arylalkyl, arylalkoxy, haloalkoxy (containing up  
 to five halo groups).

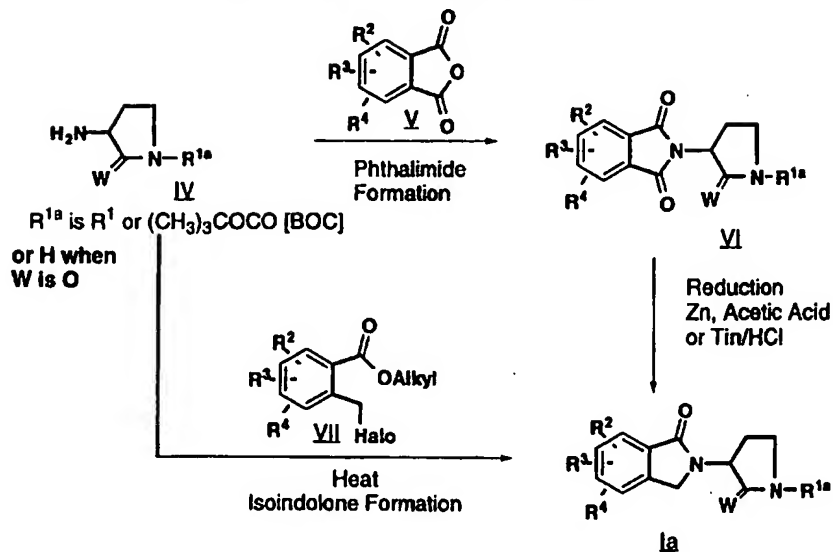
In structure II, it is also preferred that  
 R<sup>1</sup> is arylalkyl or heteroarylalkyl wherein alkyl of  
 20 each has at least 2 carbons (preferably at least 3  
 carbons) and R<sup>5</sup> and R<sup>6</sup> may be as defined  
 hereinbefore and may or may not be the preferred  
 groups set out above.

It is to be understood that combinations of  
 25 substituents which lead to chemically unstable  
 molecules are not included within the scope of the  
 present invention; for example, compounds of the  
 invention will not include -O-O-, -O-C-OH, N-C-OH  
 and -S-C-OH linkages.

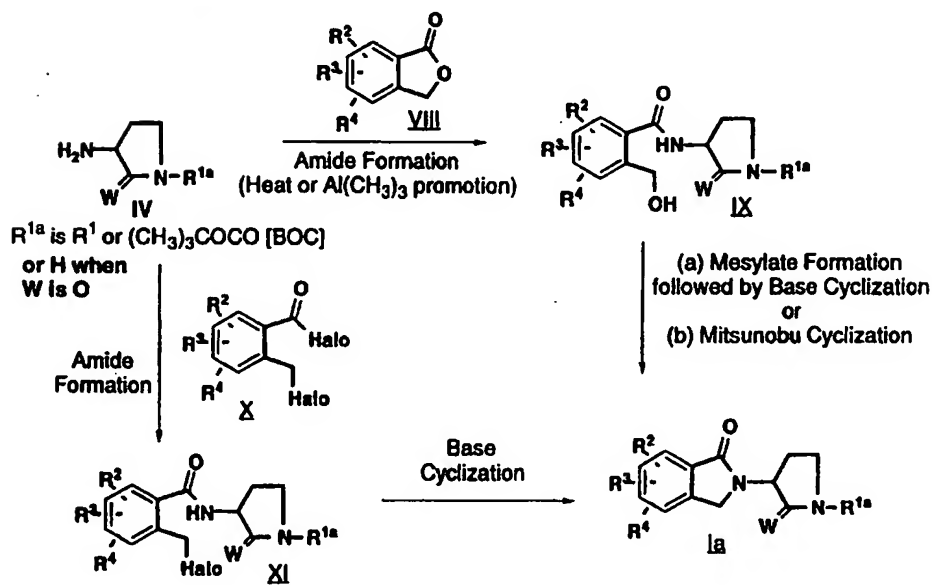
30 The compounds of formulae I and II may be  
 prepared by the exemplary processes described in  
 the following reaction schemes. Exemplary reagents  
 and procedures for these reactions appear  
 hereinafter and in the working Examples.

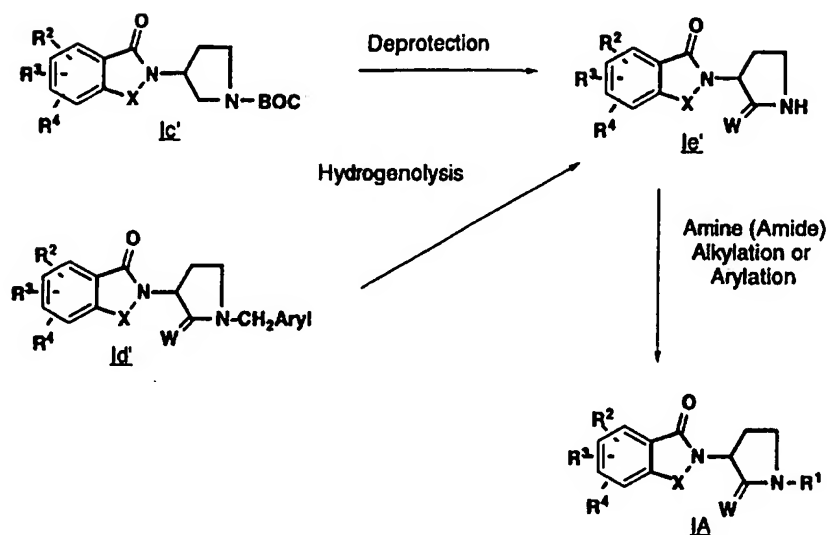
35

Scheme I. Routes to Isoindolinone Piperidines

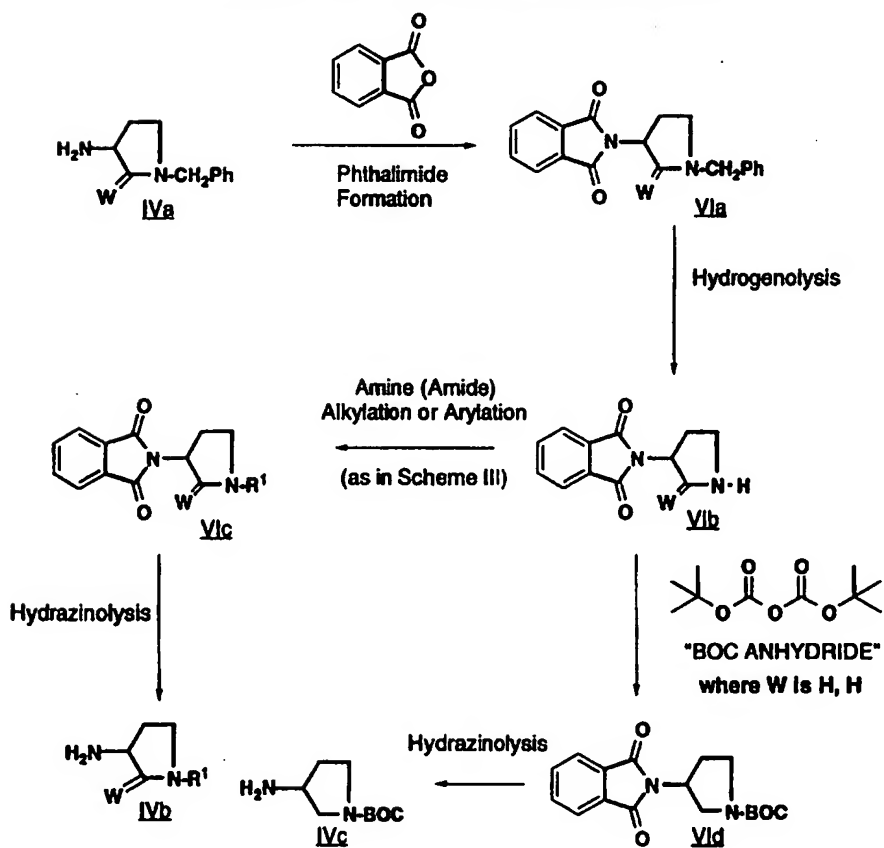


Scheme II. Additional Routes to Isoindolinone Piperidines

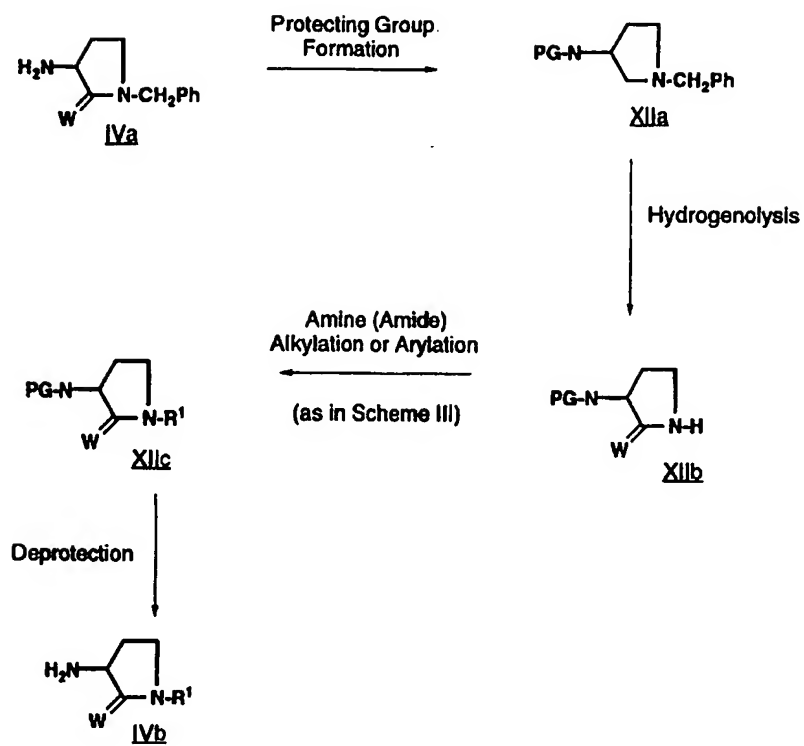


Scheme III. Introduction of R<sup>1</sup> by Alkylation or Arylation

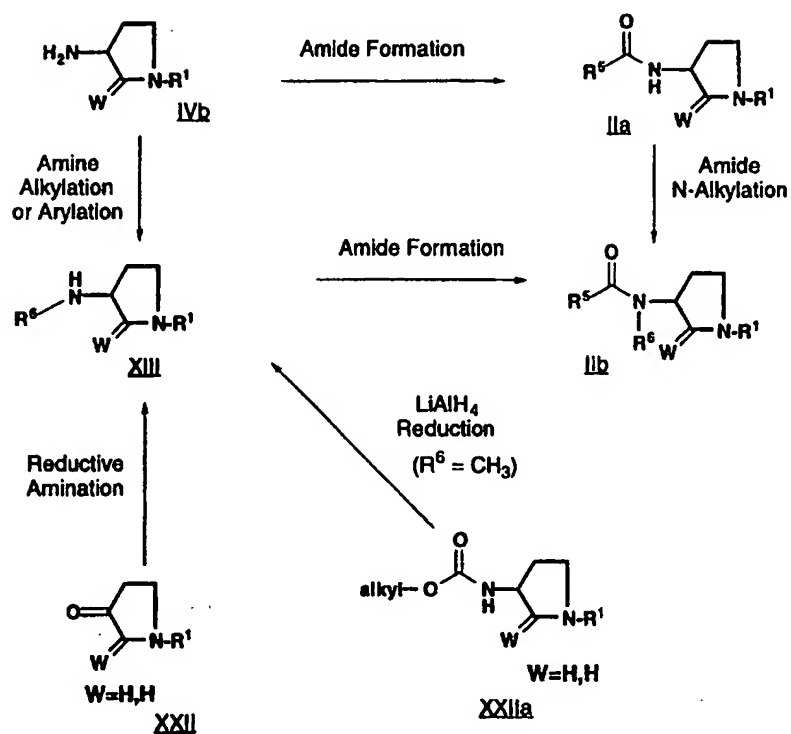
Scheme IV. Routes to Starting Materials IVb and IVc

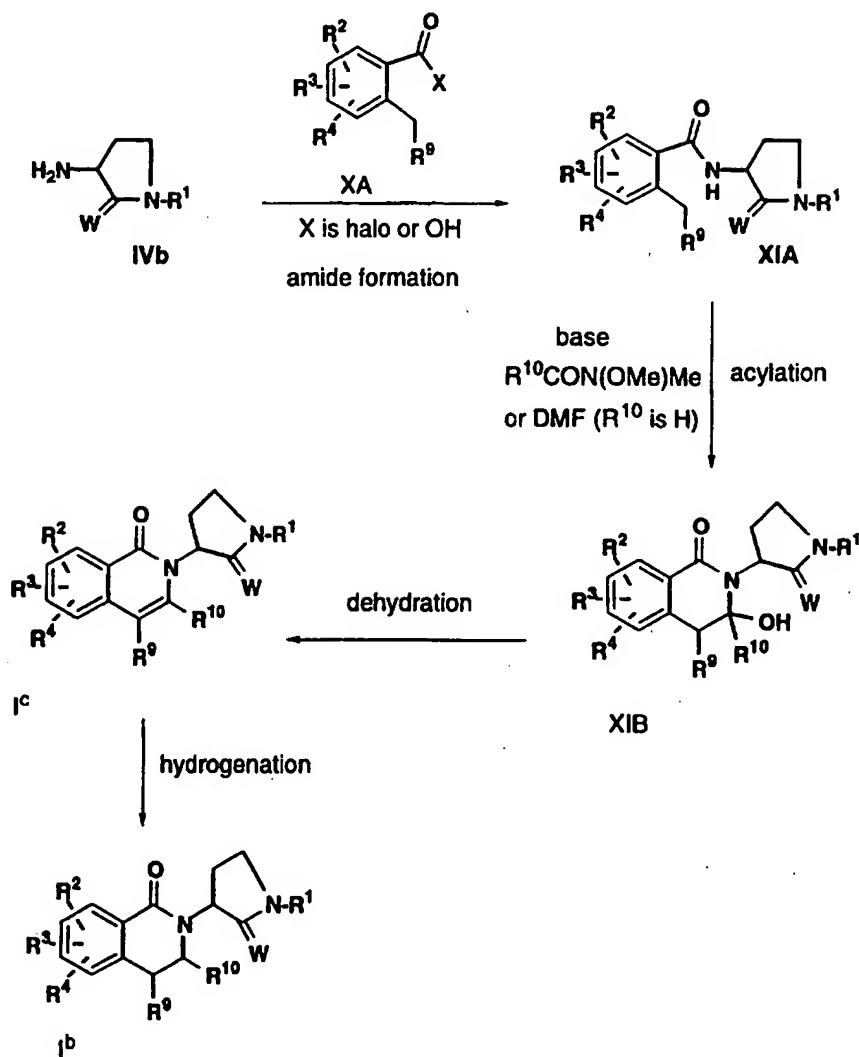


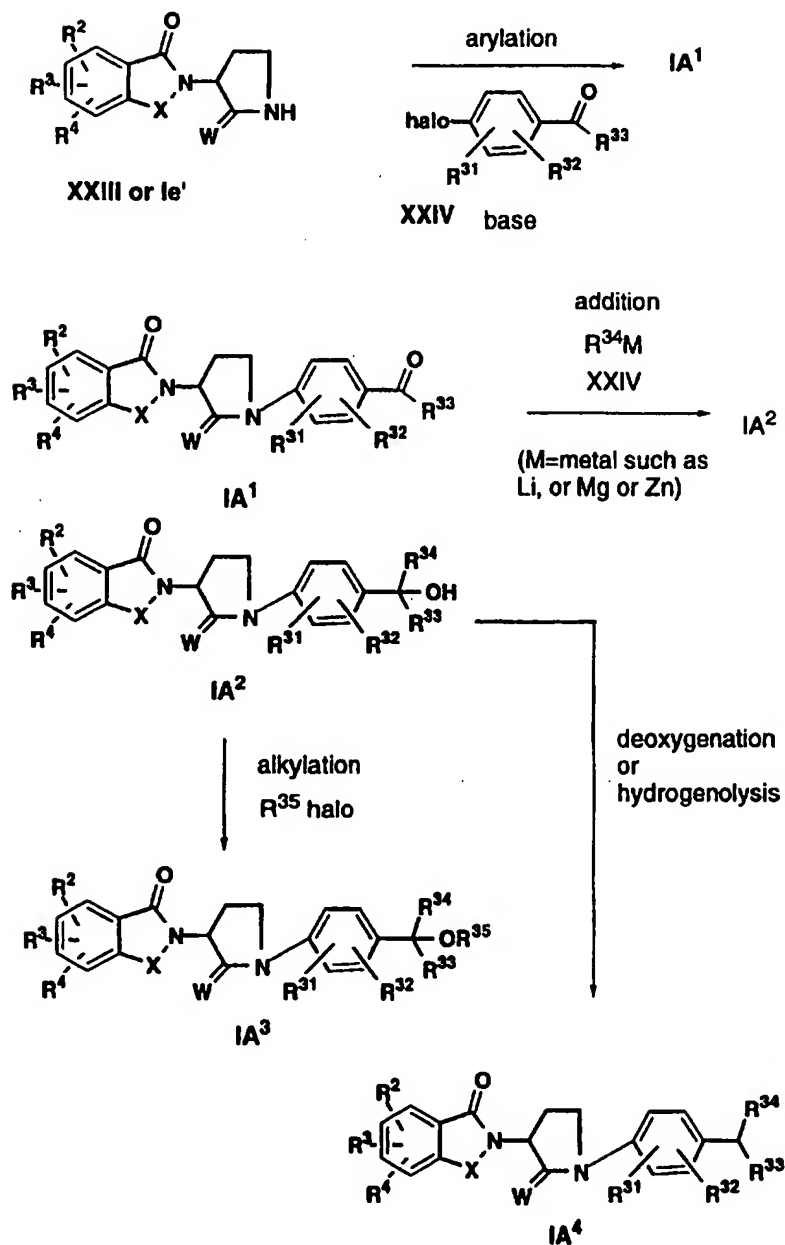
Scheme V. General Routes to Starting Materials IVb



## Schemes VI and VII. General Routes to II



Scheme VIII Preparation of Compounds I<sup>b</sup>, I<sup>c</sup>

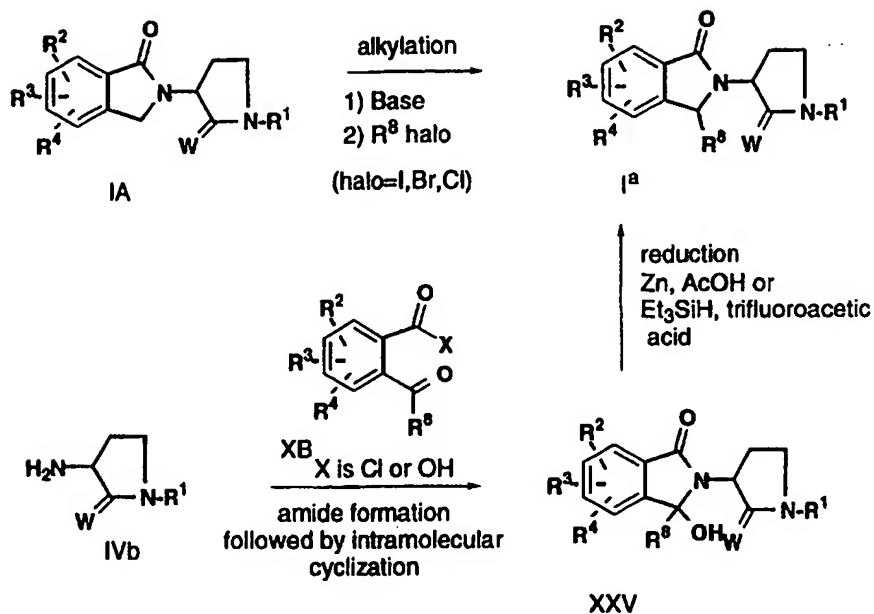
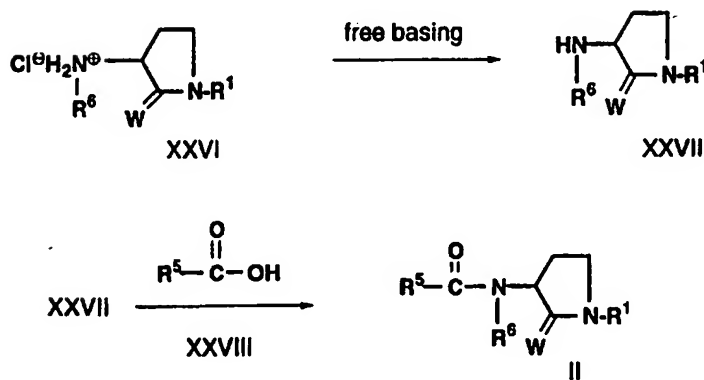
Scheme IX Preparation of Compounds IA<sup>1</sup>-IA<sup>2</sup>

R<sup>31</sup> and R<sup>32</sup> are independently selected from any of the R<sup>2</sup>, R<sup>3</sup>, or R<sup>4</sup> radicals;

5 R<sup>33</sup> and R<sup>34</sup> are independently selected from any of the R<sup>1</sup> radicals as well as aryloxy, alkoxy, arylalkoxy, heteroarylalkoxy and heteroaryloxy;

R<sup>35</sup> can be any of the R<sup>1</sup> radicals.



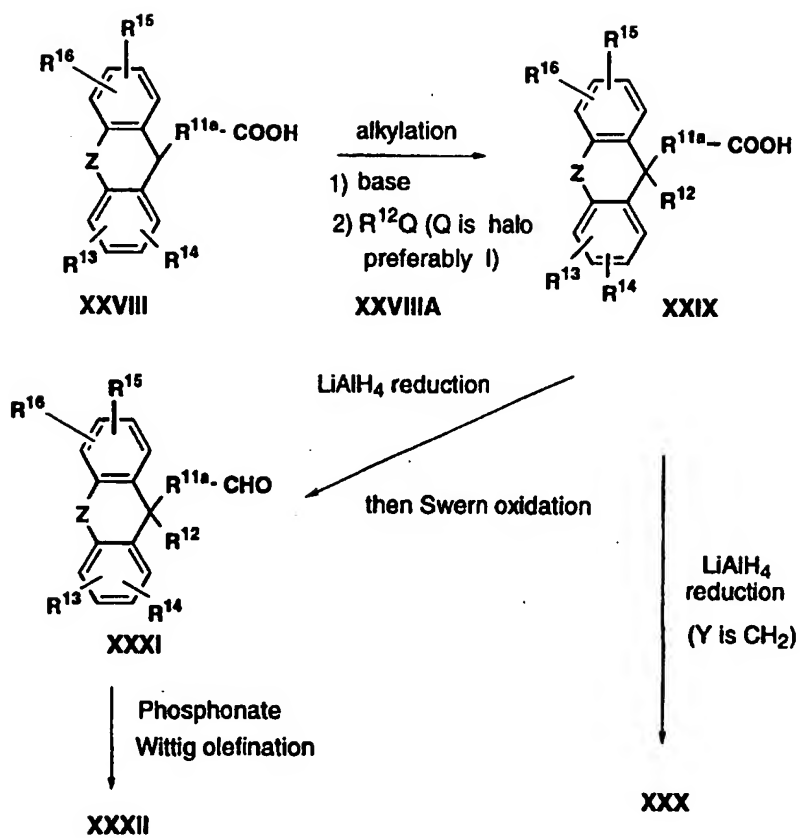
Scheme X Preparation of Compound I<sup>a</sup>Scheme XI Preparation of Compound II  
(Robotic Amide Coupling)

5 In the following Schemes XII et al, in the fluorenyl rings or fluorenyl analogs, the fused aryl groups:

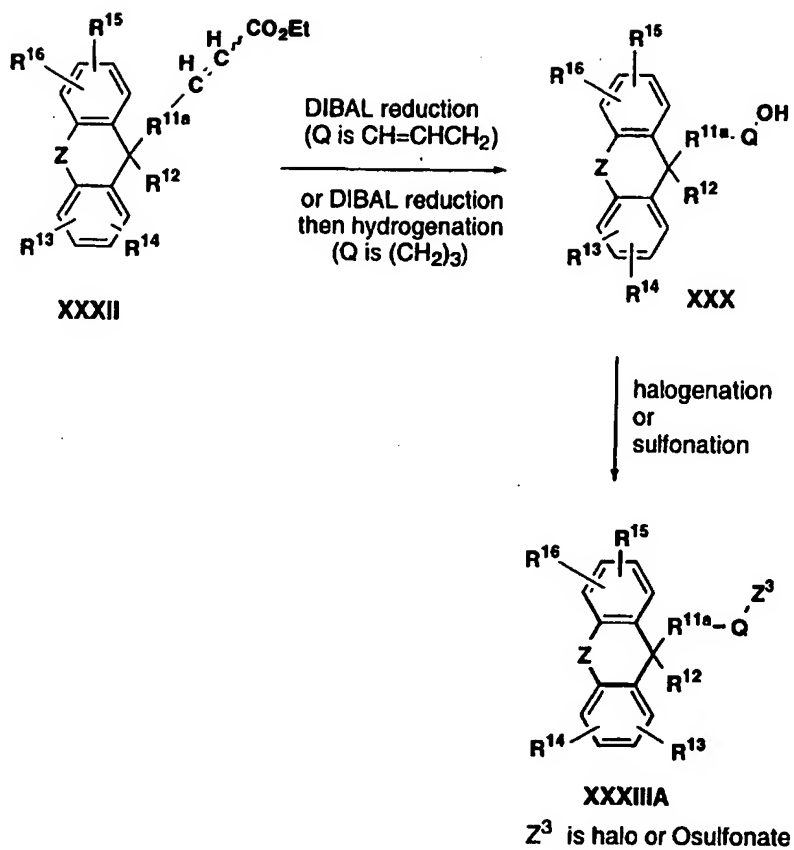


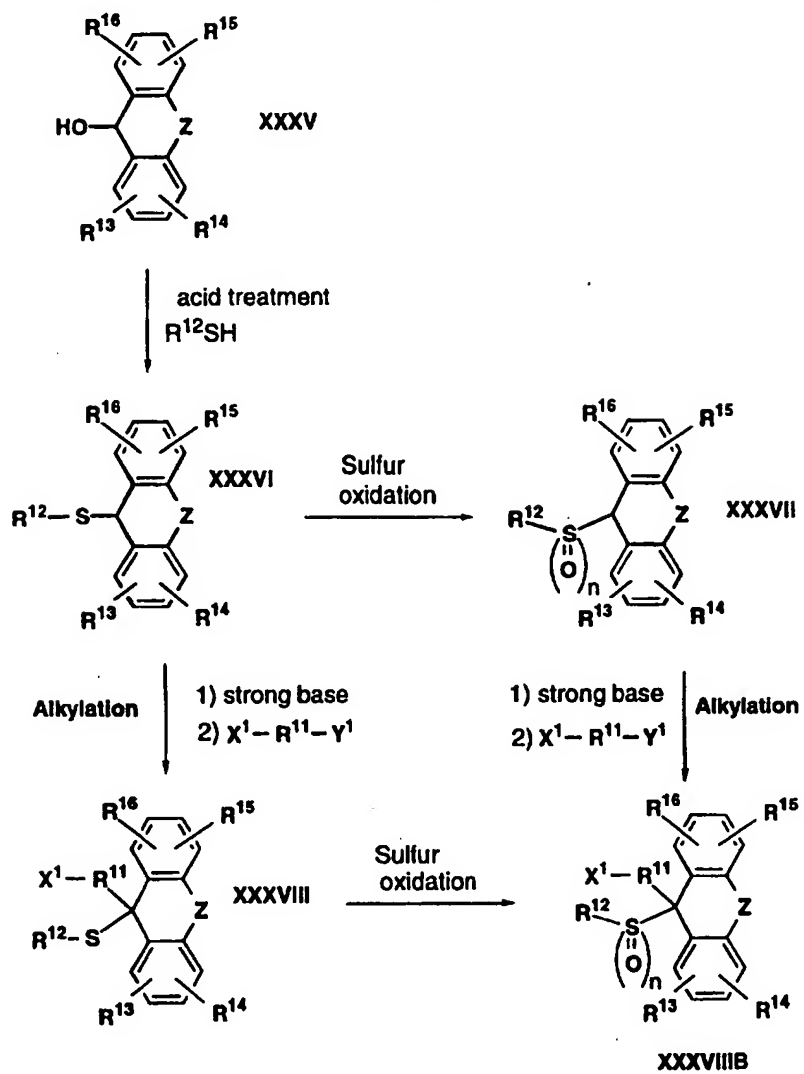
may each optionally be replaced by a 5- or 6-membered heteroaryl ring as defined herein.

## Scheme XII



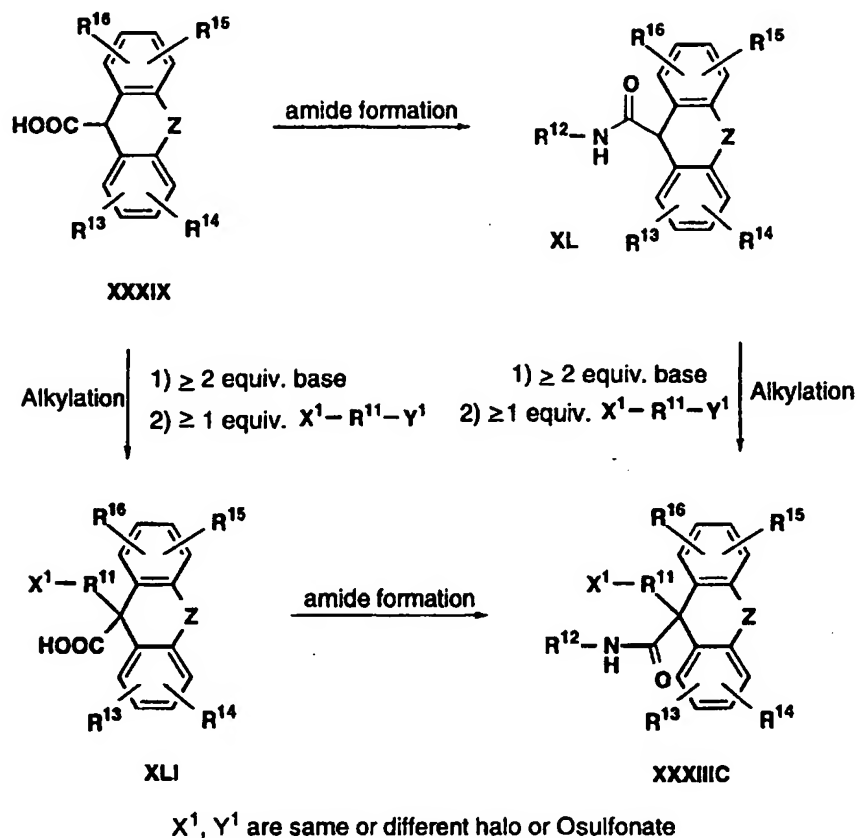
5  $R^{11a}$  can be any of the  $R^{11}$  radicals.



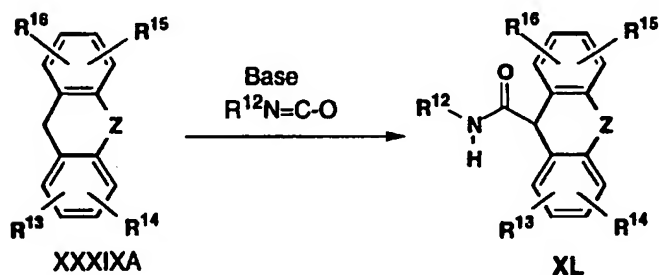
Scheme XIII - Preparation of Intermediates where  $Z^2$  is S, SO or  $SO_2$ 

$X^1, Y^1$  are same or different halo or Osulfonate

$n = 1$  or  $2$

Scheme XIVA - Preparation of A (Intermediates where  $Z^2$  is NHCO)Scheme XIVB

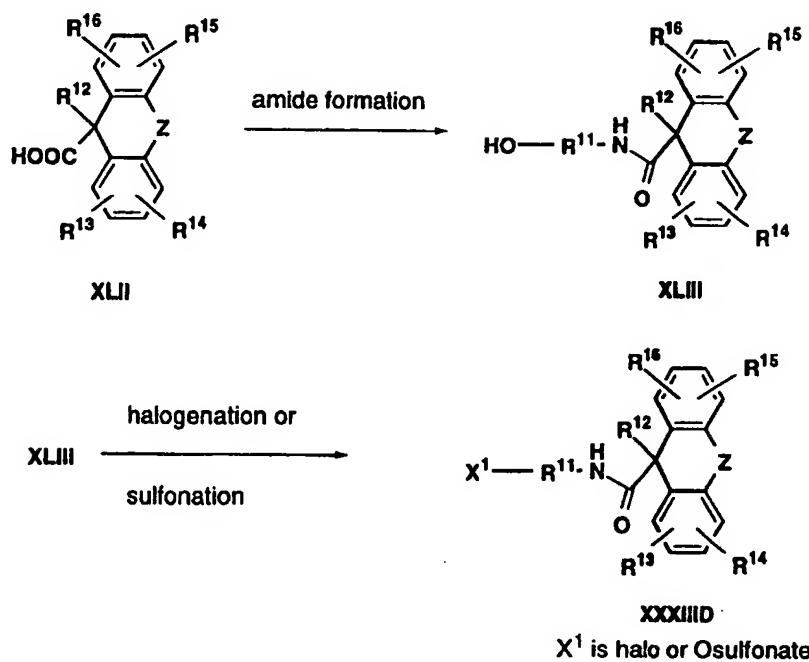
Alternative Procedure for Preparing Intermediate XL  
(Shown in Scheme XIVA)



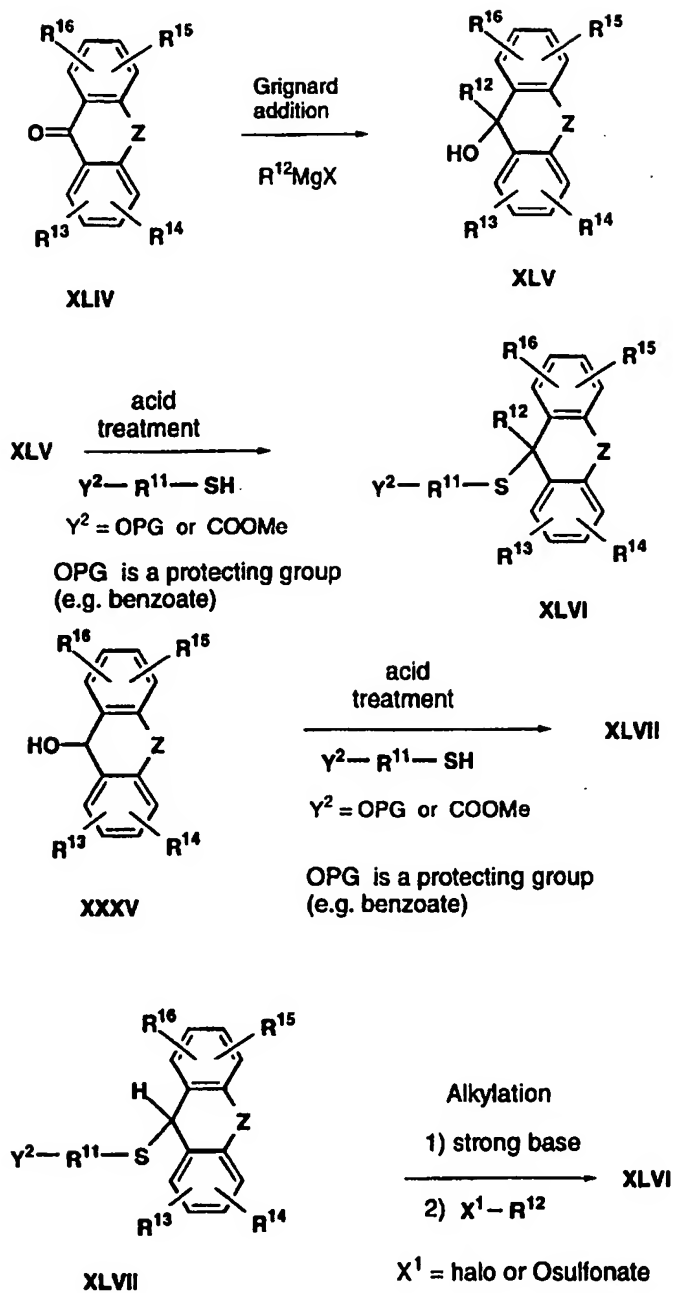
In carrying out the above reaction, bases such as *n*-butyllithium, lithium bis(trimethylsilyl) amide and sodium bis(trimethylsilyl) amide may be employed in an aprotic solvent such as THF, at between  $-78^\circ\text{C}$  and  $35^\circ\text{C}$ .

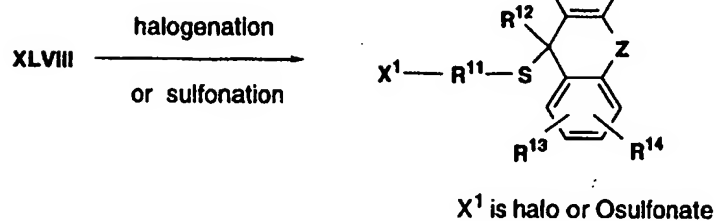
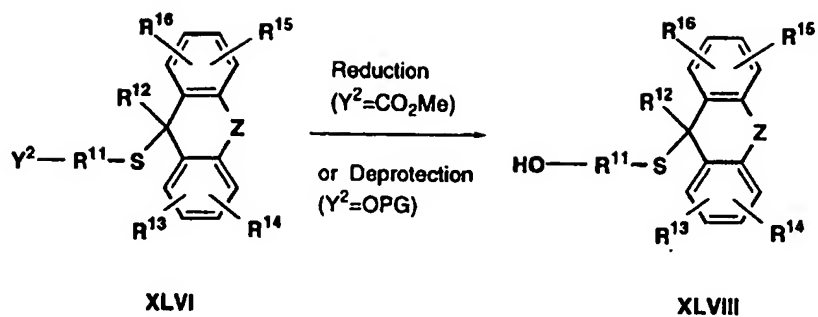
It is preferable to have the starting material and isocyanate ( $R^{12}N=C-O$ ) together in solvent, and then add the base, and optionally add further excess isocyanate subsequently.

Scheme XV - Preparation of Intermediate where  $Z^1$  is  $\begin{array}{c} \text{H} \\ | \\ -\text{N}-\text{C}- \\ || \\ \text{O} \end{array}$

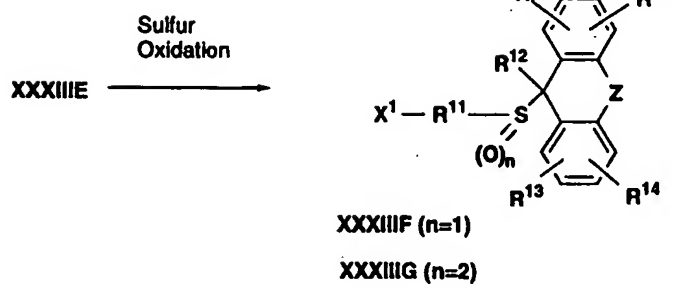


## Scheme XVI



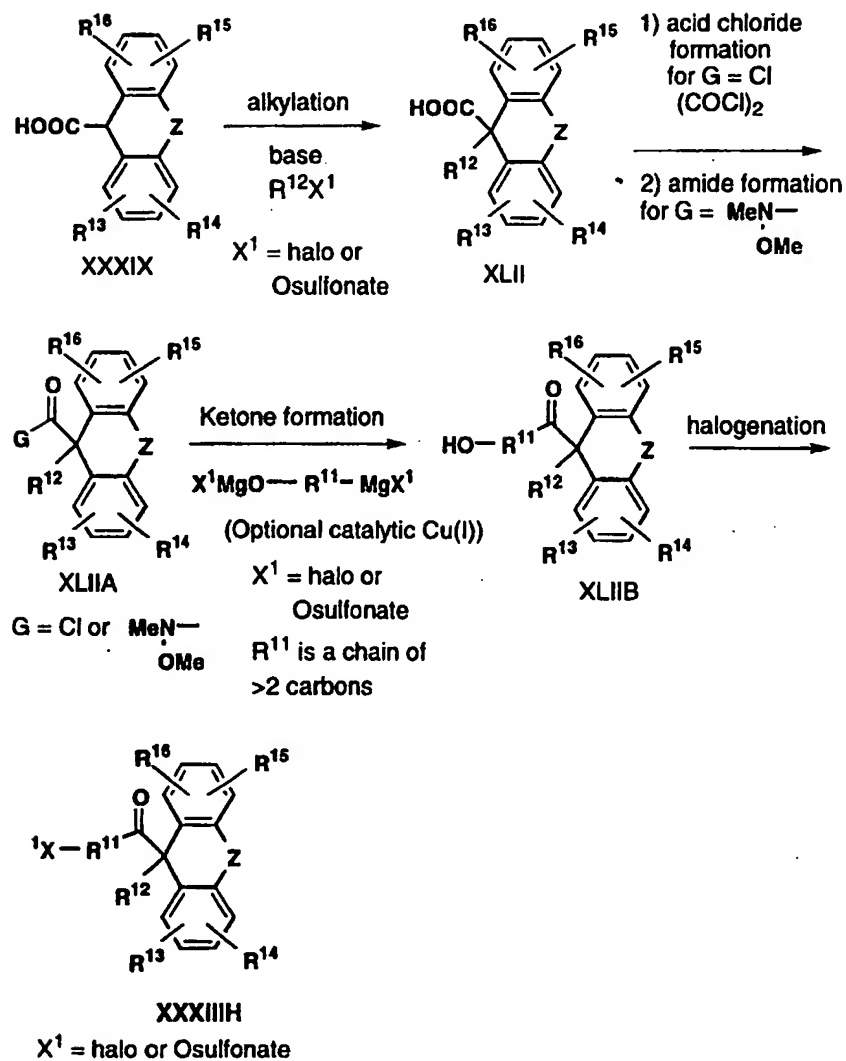


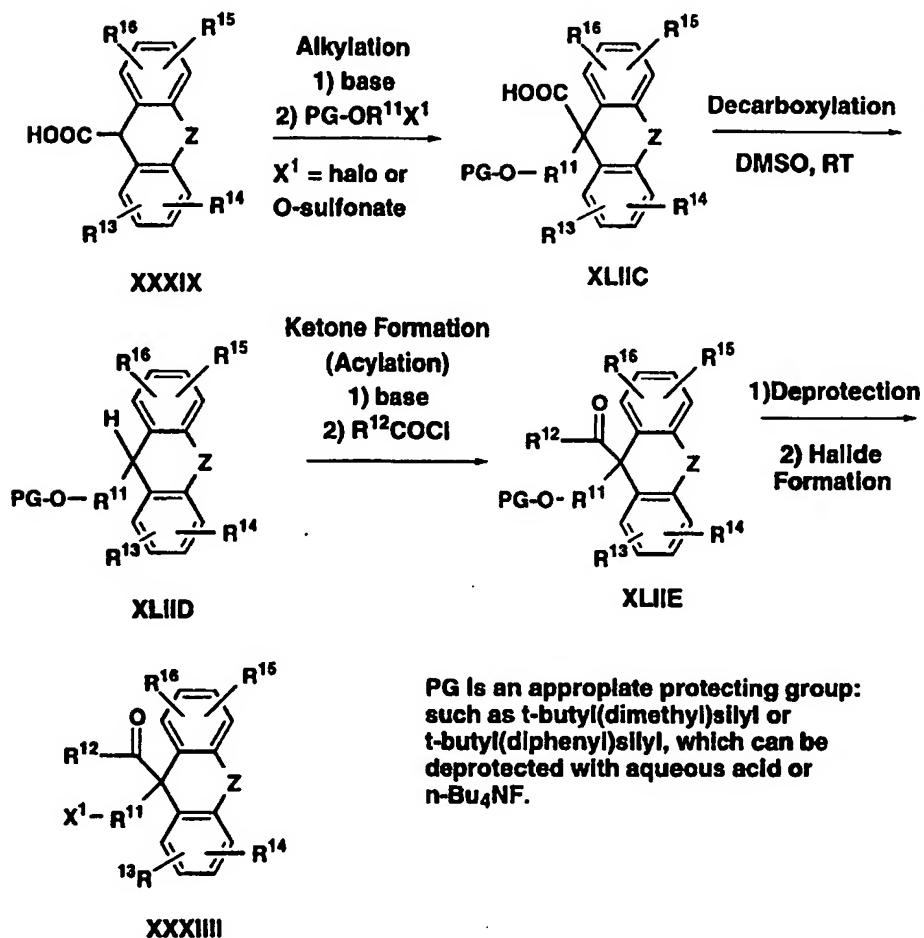
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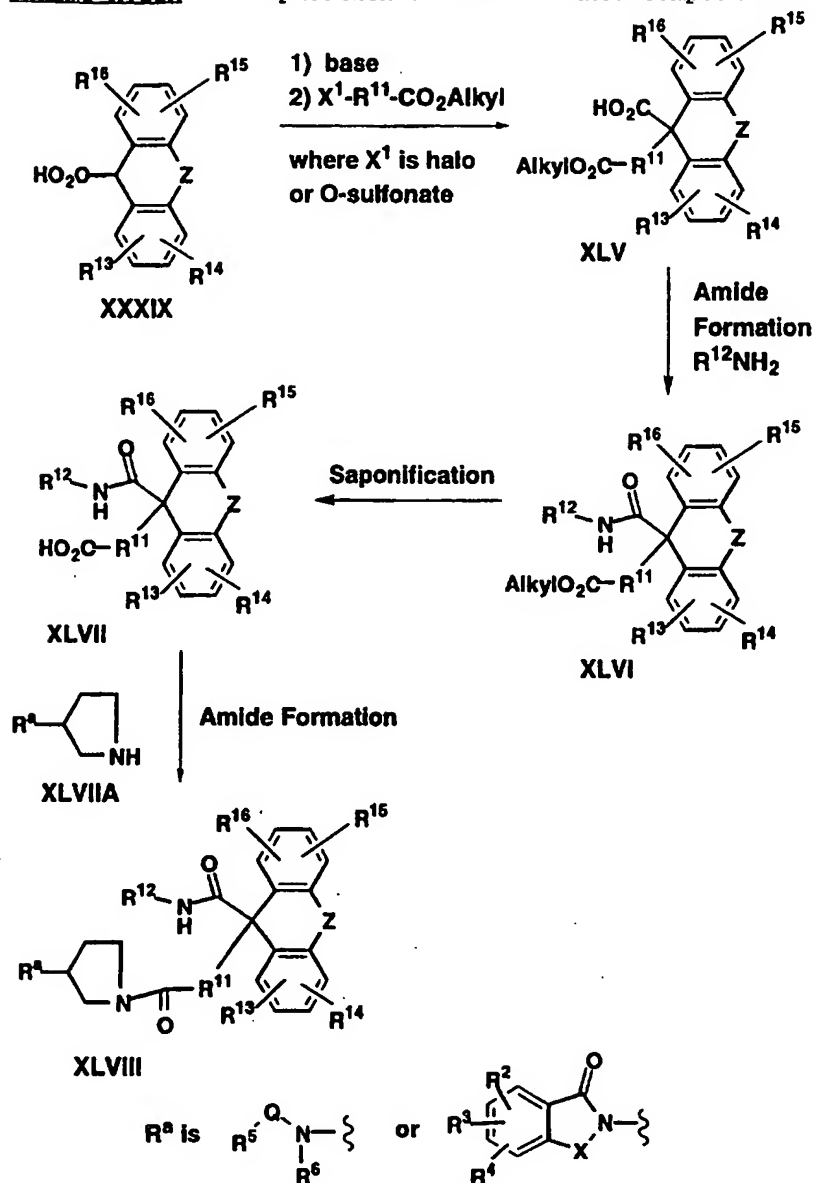


## Scheme XVIA Preparation of Ketones

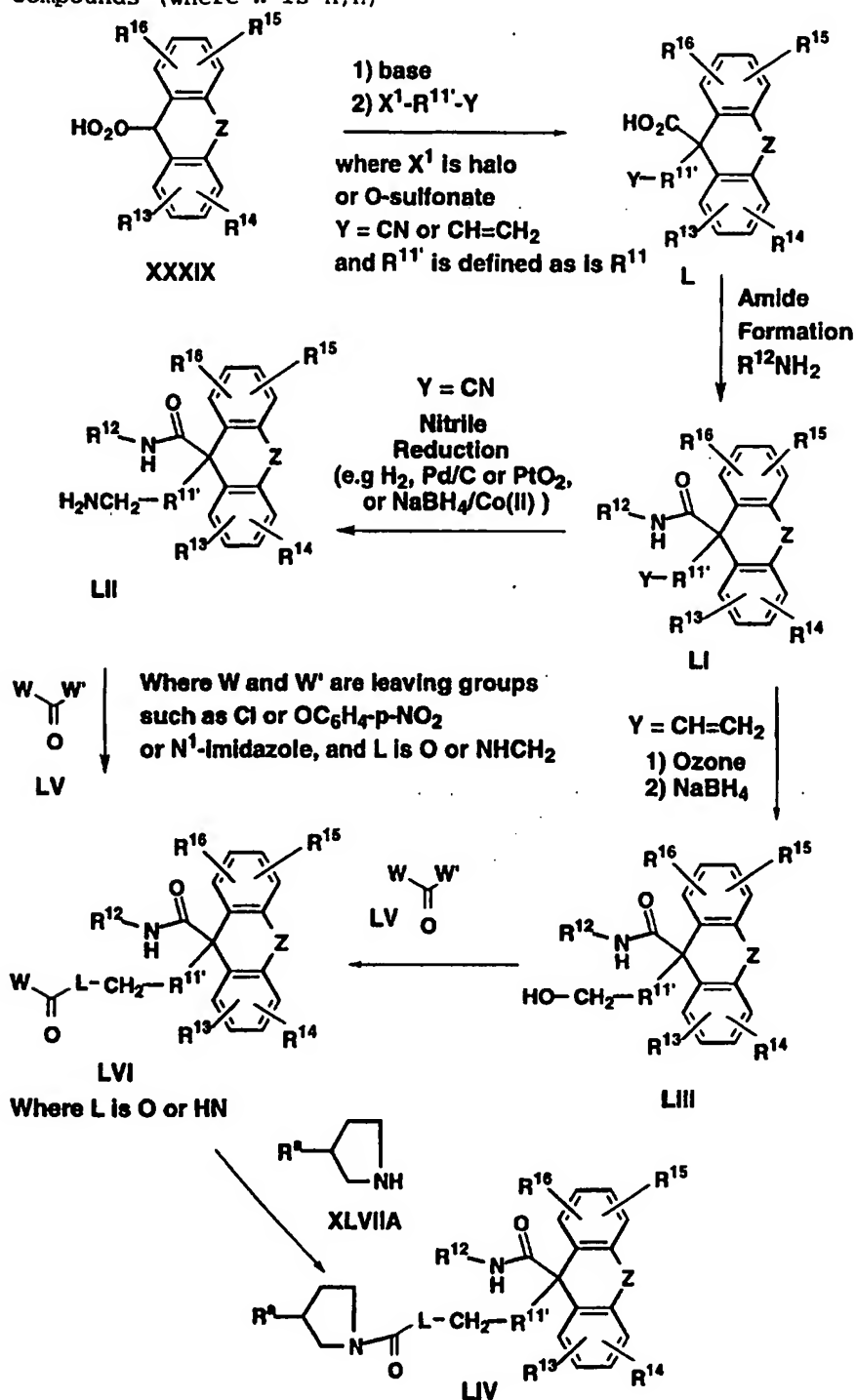


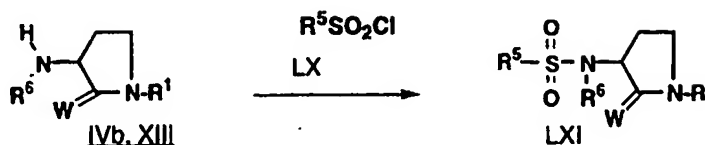
**Scheme XVI B. Preparation of Ketones (Preferred Route)**

## Scheme XVIIIA - Preparation of Amide Linked Compounds

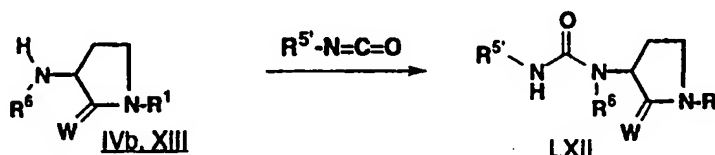


**Scheme XVIIB - Preparation of Carbamate and Urea Linked Compounds (where W is H,H)**



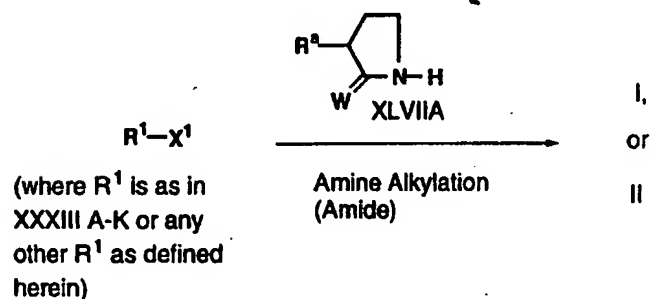
Scheme XVIII A - Formation of Sulfonamides

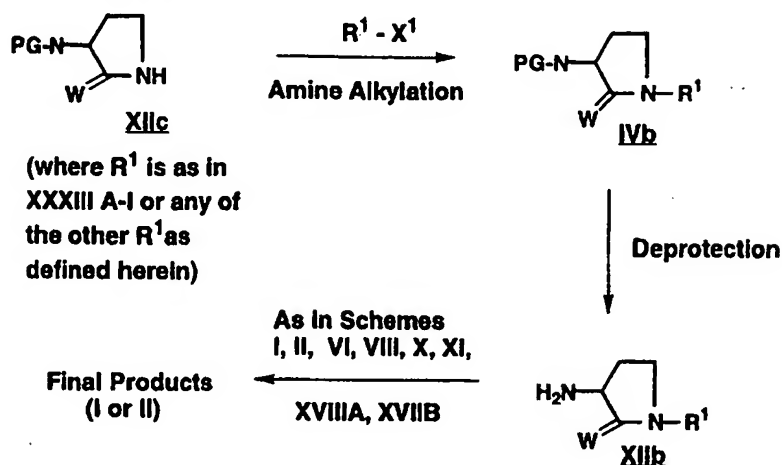
(Reaction in a variety of solvents ( $\text{CH}_2\text{Cl}_2$ , THF, pyridine) optionally in the presence of a tertiary amine base, such as pyridine or triethyl amine).

5 Scheme XVIII B - Formation of Ureas ( $\text{R}^5$  is Amino)

(1 to 10 equiv of  $\text{R-C=N=O}$ , in aprotic solvent such as toluene, from  $0^\circ\text{C}$  to  $150^\circ\text{C}$ ).

( $\text{R}^5'$  is alkyl, aryl, heteroaryl or arylalkyl).

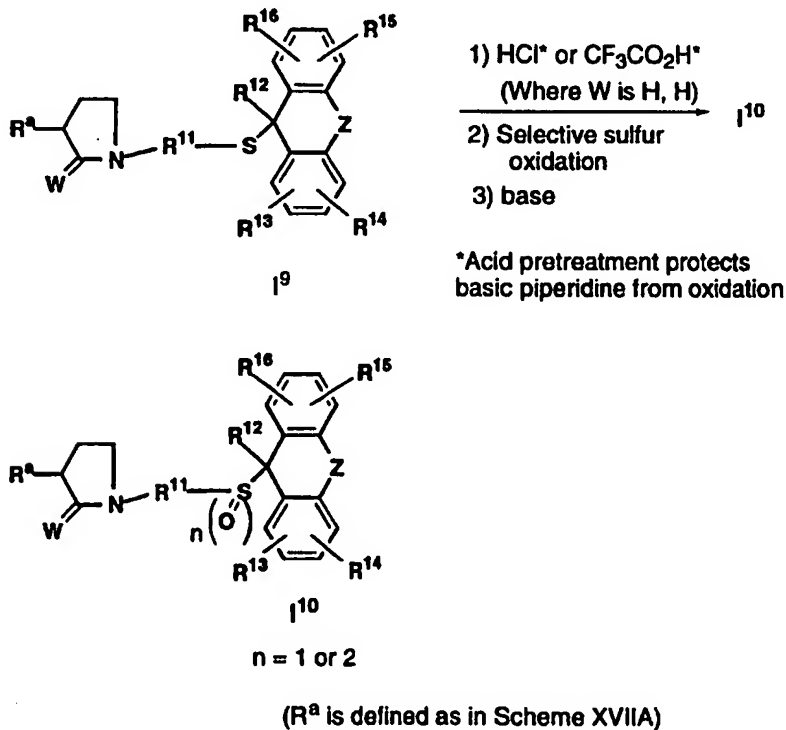
10 Scheme XIX A - General Route to Final Product

**Scheme XIXB** General Route to Final Products (I or II)

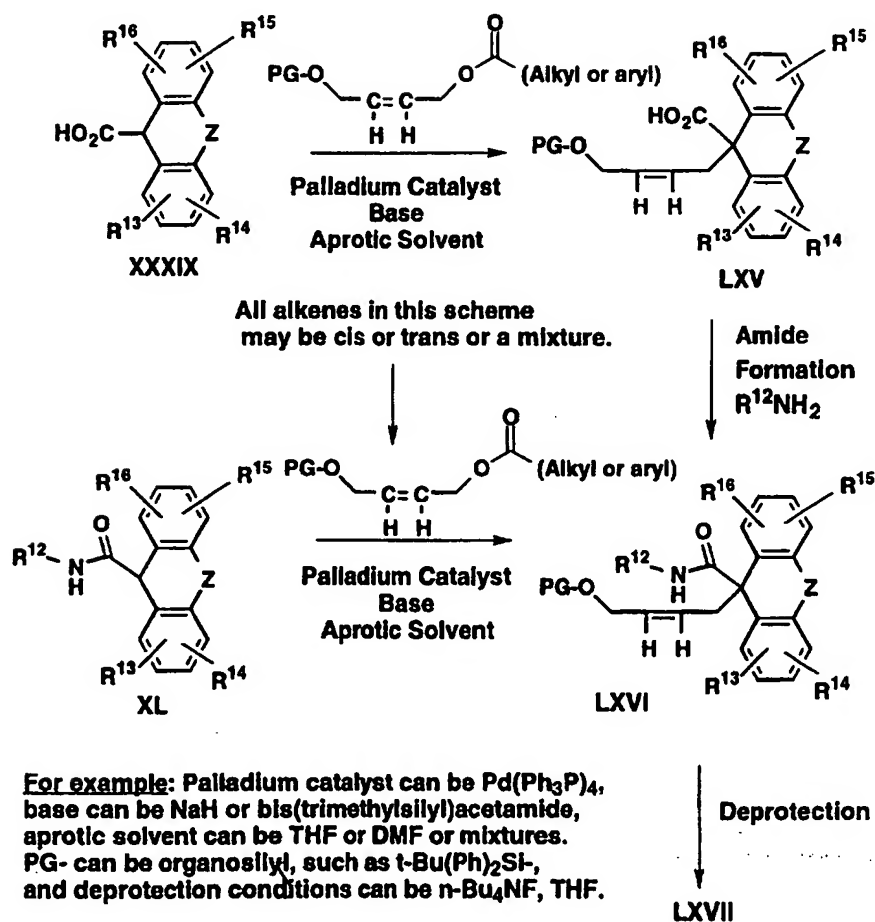
(Example of a protected nitrogen (PG-N) is the t-BuOC=ONH (BOC amino) group, which can be deprotected under mild conditions, such as anhydrous HCl in dioxane or neat trifluoroacetic acid).

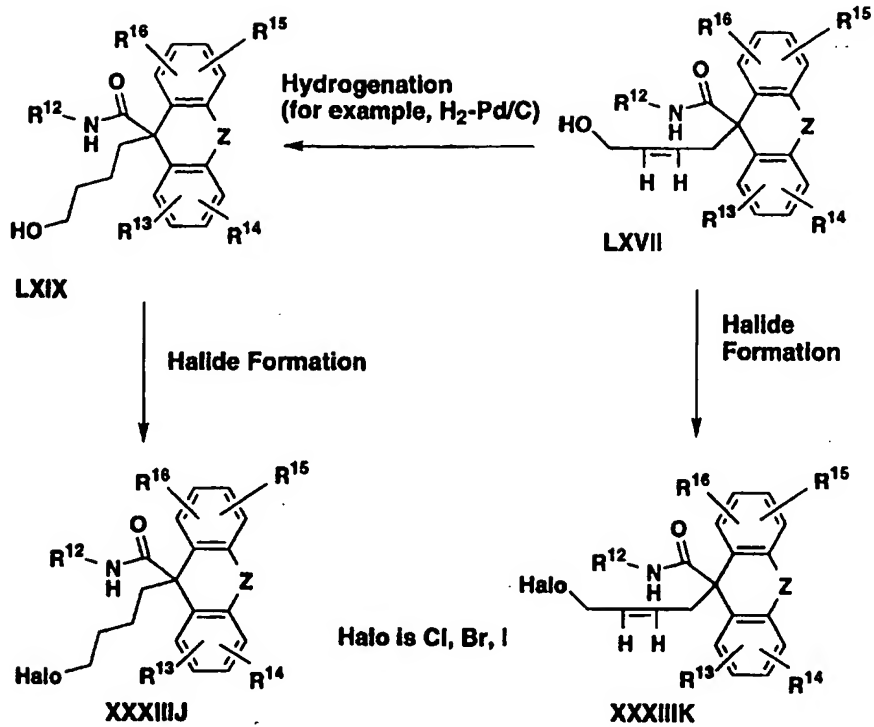
**Scheme XX** - Oxidation of sulfur at the end of the reaction sequence

5



## Scheme XXI - Preparation of Halide Intermediates

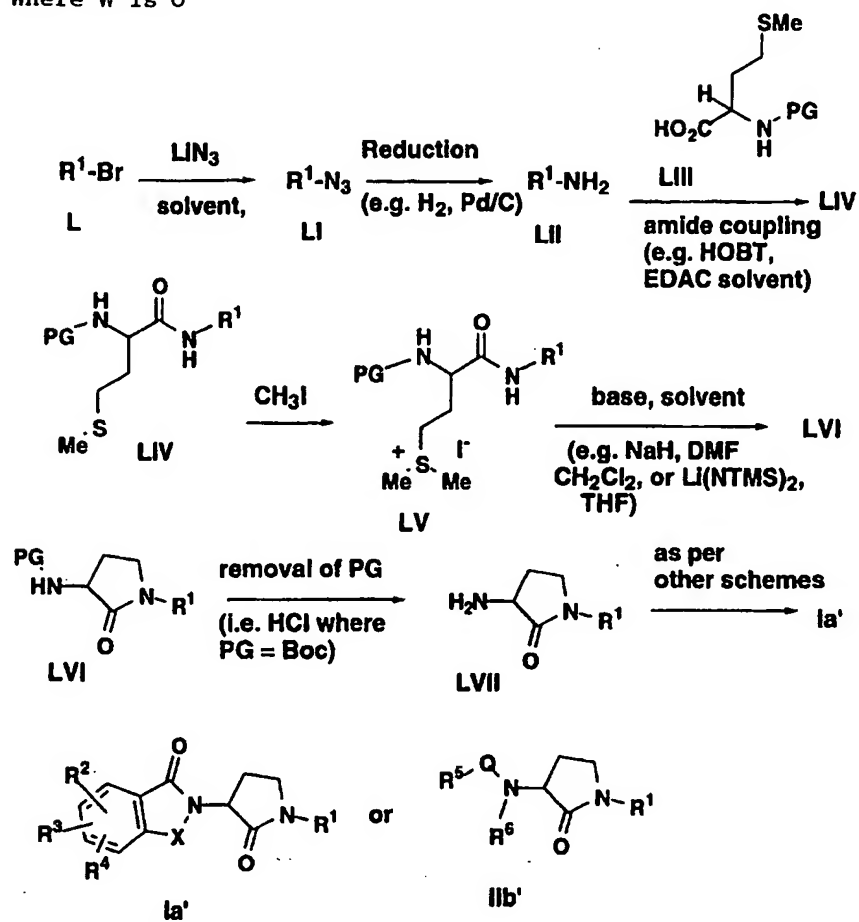




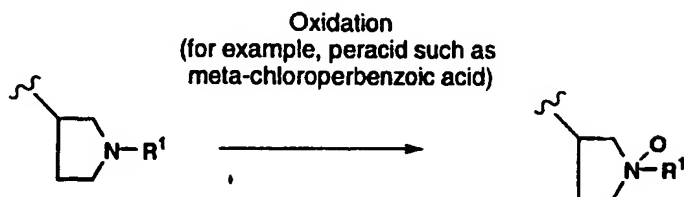


## Scheme XXII - Preparation of Formulae I and II Compounds

Where W is O



Scheme XXIII -- Preparation of N-Oxides of Formulae I and II  
Compounds



5

In the above Reaction Schemes XII through  
XXI, the starting fluorenyl-type acid XXVIII,  
alcohol XXXV, acids XXXIX and XLII, ketone XLIV,  
hydride XXXIXA, and amide XL groups may be  
10 substituted with corresponding acid, alcohol,  
ketone, hydride and amide containing fluorenyl  
type groups as set out in A, B, C and D or  
indenyl-type groups as set out in E, F, G and/or H  
to provide an intermediate compound for use in  
15 preparing a compound of formula I or II of the  
invention as per Reaction Schemes I to XXII.

Phthalimide formation (Reaction Schemes I,  
IV and XXII) may be carried out by heating to  
about 80 to 150°C in an oil bath optionally in an  
20 inert solvent or by various other procedures known  
in the art.

Reduction (Reaction Schemes I, XXII) may be  
carried out by treatment with such reducing agents  
as zinc in the presence of acetic acid or tin in  
25 the presence of hydrochloric acid under an inert  
atmosphere (e.g., argon).

Isoindolone formation (Reaction Schemes I,  
XXII) may be carried out by heating in the range  
of about 50 to 150°C in an organic solvent (e.g.,  
30 toluene, ethanol, dimethylformamide) optionally in  
the presence of a salt (e.g., potassium carbonate)  
or a tertiary amine base (e.g., 2,6-di-*t*-butyl-  
pyridine or triethylamine).

Amide formation (Reaction Schemes II, VI, VII, VIII, X, XI, XIVA, XV, XVI, XVIA, XVIB, XVIIA, XVIIB, XXI, XXII), may be carried out by a number of methods known in the art. For example,

5 an amine substrate may be treated with (1) an acid halide  $R^5C(O)halo$  or compound X or XA in an aprotic solvent, optionally in the presence of a tertiary amine base (e.g., triethylamine); (2) the acid halide in the presence of an aqueous base under

10 Schotten-Baumann conditions; (3) a free carboxylic acid ( $R^5CO_2H$ ) in the presence of a coupling agent such as dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

15 (WSC), optionally in the presence of 1-hydroxybenzotriazole (HOBT); (4) the free acid in the presence of N, N-carbonyldiimidazole in an aprotic organic solvent followed by the amine substrate; (5) trialkylaluminum (e.g.,  $Al(CH_3)_3$ ) in an aprotic

20 solvent, followed by an ester (e.g.,  $R^5CO_2alkyl$  or compound VIII) or (6) mixed anhydride formation, by reacting the acid with an acid chloride (e.g., isobutyl chloroformate or bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (Bop-Cl)) in the

25 presence of a tertiary amine base (e.g., triethylamine) followed by treatment with the amine substrate.

Mesylate formation (Reaction Scheme II) may be carried out by treatment of the amine-alcohol

30 substrate with methanesulfonyl chloride and triethylamine or pyridine or in an aprotic solvent, such as dichloromethane.

Base cyclization (Reaction Schemes II, VIII, XXII) may be carried out by treatment with a

35 base (e.g., potassium *t*-butoxide, lithium hexamethyldisilazide ( $LiN(TMS)_2$ ) or sodium hydride) in an inert solvent (e.g., dimethylformamide,

tetrahydrofuran, dimethoxymethane, or toluene). Mitsunobu cyclization (Reaction Scheme II) may be carried out by procedures generally known in the art. See, e.g., R. K. Olsen, J. Org. Chem., **49**, 3527 (1984); Genin, M. J., et al., J. Org. Chem., **58**, 2334-7 (1993).

Alternatively, a mixture of compounds IV and VIII can be converted to compound Ia in a single pot by heating the mixture in a protic solvent (e.g., water, methanol, ethenyl or isopropanol or mixtures thereof) at 100 to 200°C. See, e.g., European patent application 81/26,749, FR 2,548,666 (1983).

Protection and deprotection (Reaction Schemes III, IV, V, XVI, XVII, XIXB, XXI, XXII) may be carried out by procedures generally known in the art. See, for example, T. W. Greene, Protecting Groups in Organic Synthesis, Second edition, 1991. PG in Scheme V denotes a nitrogen-protecting group. One particularly useful group is tert-butoxycarbonyl (BOC) which can be derived from the associated anhydride as shown in Scheme IV. BOC-protected amines may typically be deprotected by treatment with acid (e.g., trifluoroacetic acid or hydrochloric acid) in procedures well understood by those having ordinary skill in the art.

Hydrogenolysis (Reaction Schemes III, IV, V) may be carried out with H<sub>2</sub> using a balloon apparatus or a Parr Shaker in the presence of a catalyst (e.g., palladium on activated carbon).

Amine/Amide alkylation and arylation (Reaction Schemes III, IV, V, IX, XII, XIXA, XIXB) may be carried out by methods known in the art. Suitable procedures are described in Cortizo, L., J. Med. Chem. **34**, 2242-2247 (1991). For example, the alkylation or arylation may be carried out by

treating the amine substrate with a halide (e.g.,  $R^1$ -halo) or an oxytosylate (e.g.,  $R^1$ -O-tosylate) in an aprotic solvent (e.g., dimethylformamide), optionally in the presence of a tertiary amine (e.g., triethylamine), an inorganic base (e.g., potassium carbonate, NaH), or lithium hexamethyldisilazide).

Reductive amination may be employed as an alternative to the foregoing amine alkylation and arylation procedures where W is H, H when  $R^1$ ,  $R^6$  or  $R^7$  is  $R^9R^{10}CH-$  and  $R^9$  and  $R^{10}$  are each independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl, or  $R^9$  and  $R^{10}$  together are alkylene (i.e.,  $R^9R^{10}CH-$  forms a cycloalkyl group). Such reductive amination may be carried out by treating the amine with (a) a ketone or aldehyde ( $R^9-C(O)-R^{10}$ ), (b)  $NaBH_4$ ,  $NaBH_3CN$  or  $NaB(acetoxy)_3H$ , (c) a protic solvent (e.g., methanol) or a dipolar aprotic solvent (e.g., acetonitrile), and, optionally, (d) an acid (e.g., acetic acid, trifluoroacetic acid, hydrochloric acid, or titanium isopropoxide). When  $R^1$  is aryl or heteroaryl, transition metals (e.g., palladium or copper salts or complexes) may be used to promote the arylation reaction.

Alkylation of the isoindolone (Reaction Scheme X, XXII) may be carried out by treatment of the isoindolone with a strong base (i.e. sodium bis(trimethylsilyl)amide or lithium diisopropylamide) followed by an alkyl halide (e.g.  $R^8$ -halo) or alkyl sulfonate (e.g.  $R^8$ -tosylate) in an inert solvent (e.g. tetrahydrofuran or dimethoxyethane). Alternatively, as seen in Scheme X, amine IVb can be treated under amide formation conditions with a ketone with the structure XB to provide a hydroxylactam XXV, which could be

subjected to reduction conditions with such reducing agents as zinc in acetic acid or triethylsilane in trifluoroacetic acid to give Ia.

Hydrazinolysis of phthalimides may be carried out by standard means known in the art. See, e.g., T. W. Greene, Protecting Groups in Organic Synthesis, Second edition, 1991.

Amide N-alkylation (Reaction Scheme VI, XXII) may be carried out by base treatment (e.g., NaH, KH, KN[Si(CH<sub>3</sub>)<sub>3</sub>]<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, P4-phosphazene base, or butyl lithium) in an aprotic organic solvent, followed by treatment with R<sup>6</sup>-halo or R<sup>6</sup>-O-tosylate. Use of P-phosphazene base is described in T. Pietzonka, D. Seebach, Angew. Chem. Int. Ed. Engl. **31**, 1481, 1992.

Compound III can also be prepared from compound XX as described by Cortizo, L., J. Med. Chem. **34**, 2242-2247 (1991).

Dehydration (Scheme VIII) may be carried out employing a strong acid such as hydrochloric acid, sulfuric acid or trifluoroacetic acid.

Hydrogenation (Scheme VIII) may be carried out in the presence of a conventional catalyst such as Pd/C or Pt or Rh under a H<sub>2</sub> atmosphere.

The addition reaction shown in Scheme IX may be carried out by treating Ia<sup>1</sup> with an organometallic reagent XXIV, such as an organolithium or organic magnesium compound where organo is alkyl or aryl.

The deoxygenation or hydrogenation reaction (Scheme IX) is carried out in the presence of a strong acid such as trifluoroacetic acid or boron trifluoride etherate, in the presence of a hydride source such as triethyl silane or tris(trimethylsilyl)silane.

The alkylation in Schemes XII, XIII, XIV, XVI, XVII, XVIII is carried out in the presence of

base such as butyllithium or sodium bis(trimethylsilyl)amide. It will be appreciated that  $R^{12}$  in  $R^{12}Q$  may be any of the  $R^{12}$  groups as defined hereinbefore.

- 5 Alternatively, the alkylation in the above Schemes can be performed where either or both  $Z^1$  or  $Z^2$  is a bond, using a palladium catalyzed allylic alkylation procedure. In this reaction, the fluorenyl-type or indenyl-type precursors
- 10 (compounds XXVIII, XXXVI, XXXVII, XXXIX, XL, XLVII) are reacted with a base (sodium hydride, sodium bis(trimethylsilyl)amide or bis(trimethylsilyl)acetamide), a palladium catalyst (for example  $Pd(Ph_3)_4$ ) and an allylic
- 15 acetate ( $CH_3CO_2CH_2-CH=CH-$  or  $CH_3CO_2CH-CH=CH_2$ ) in an inert solvent (for example THF). This reaction is to introduce either  $-R^{12}$  (Scheme XII) or  $-R^{11}-X^1$  (Schemes XIII, XIV, XVI, XVII) or  $-R^{11}-OPG$  (Scheme XVIB, Scheme XXI). The product of this reaction
- 20 contains either an  $-R^{12}$  group or an  $-R^{11}-X^1$  group (or an  $-R^{11}-OPG$  group) which begins with  $-CH_2-CH=CH-$ . Saturation of the alkene in  $R^{11}$  or  $R^{12}$  can be accomplished by standard catalytic hydrogenation conditions.

- 25 With respect to Scheme XII, the  $LiAlH_4$  reduction, Swern oxidation, Wittig olefination and halogenation/sulfonation reactions are conventional reactions well known to those skilled in the art.

- 30 The sulfur oxidation in Schemes XIII, XVI and XVIII is carried out as follows.

- Sulfides of structures XXXVI, XXXVIII, XXXIIIE and  $I^9$  can be selectively oxidized to sulfoxides by 1 molar equivalent of reagents known
- 35 in the art, such as 30%  $H_2O_2$ ,  $NaIO_4$ , and peracids (e.g., meta-chloroperbenzoic acid). The resulting sulfoxides can be further transformed to

corresponding sulfones by another molar equivalent or excess of 30% H<sub>2</sub>O<sub>2</sub>, KMnO<sub>4</sub>, KHSO<sub>5</sub>, or peracids (e.g., meta-chloroperbenzoic acid). Alternatively, the sulfones can be directly prepared from

5 sulfides with 2 molar equivalents or more of oxidizing agents, such as 30% H<sub>2</sub>O<sub>2</sub> and peracids (e.g., meta-chloroperbenzoic acid). In cases where an amine (such as a pyrrolidine in I<sup>9</sup>) is present during the oxidation, the basic nitrogen

10 may be protected by pretreatment with an acid such as HCl or CF<sub>3</sub>CO<sub>2</sub>H (see Scheme XIX).

To prepare examples where Z<sup>1</sup> or Z<sup>2</sup> is -CHOH, the compounds I and II where Z<sup>1</sup> or Z<sup>2</sup> is C=O can be reduced with a hydride reagent, for example NaBH<sub>4</sub>.

15 The compounds of the invention may be employed in preventing, stabilizing or causing regression of atherosclerosis in a mammalian species by administering a therapeutically effective amount of a compound to decrease the

20 activity of MTP.

The compounds of the invention can be tested for MTP inhibitory activity employing the procedures set out in U.S. application Serial No. 117,362 filed September 3, 1993, employing MTP

25 isolated from one of the following sources:

- (1) bovine liver microsomes,
- (2) HepG<sub>2</sub> cells (human hepatoma cells) or
- (3) recombinant human MTP expressed in baculovirus.

30 The compounds of the invention may also be employed in lowering serum lipid levels, such as cholesterol or triglyceride (TG) levels, in a mammalian species, by administering a therapeutically effective amount of a compound to

35 decrease the activity of MTP.

The compounds of the invention may be employed in the treatment of various other



conditions or diseases using agents which decrease activity of MTP. For example, compounds of the invention decrease the amount or activity of MTP and therefore decrease serum cholesterol and TG levels, and TG, fatty acid and cholesterol absorption and thus are useful in treating hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, pancreatitis, hyperglycemia and obesity.

10           The compounds of the present invention are agents that decrease the activity of MTP and can be administered to various mammalian species, such as monkeys, dogs, cats, rats, humans, etc., in need of such treatment. These agents can be  
15 administered systemically, such as orally or parenterally.

          The agents that decrease the activity or amount of MTP can be incorporated in a conventional systemic dosage form, such as a  
20 tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physiologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol),  
25 anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

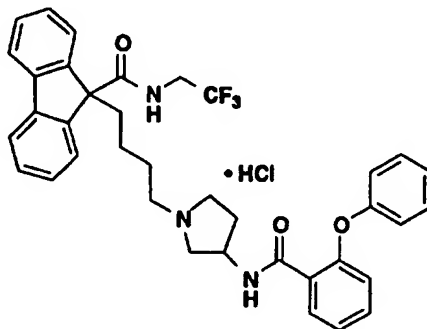
          The dose administered must be carefully  
30 adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms described above may be administered in amounts of  
35 from about 5 to about 500 mg per day in single or divided doses of one to four times daily.

The following Examples represent preferred embodiments of the invention. All temperatures are in °C unless indicated otherwise.

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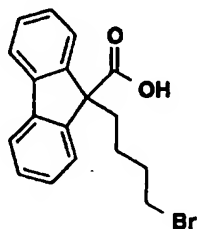
**Example 1**

9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride



10

A.



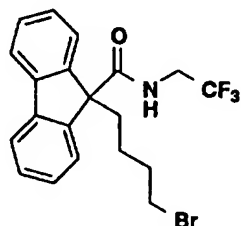
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To a solution of 9-fluorenenecarboxylic acid (50 g, 240 mmol) in THF (1200 mL) at 0°C was added dropwise a solution of n-butyllithium (2.5M, 211 mL, 530 mmol) in THF. The yellow reaction was stirred at 0°C for 1 h, then 1,4-dibromobutane (31.3 mL, 260 mmol) was added dropwise over 30 min. The reaction was stirred at 0°C for 30 min, then the reaction was warmed to RT for 30 h. The reaction was extracted with water (3 x 750 mL). The combined aqueous layers were extracted with ethyl ether (800 mL). The aqueous layer was made acidic with HCl solution (1N, 500 mL), then

extracted with dichloromethane (3 x 750 mL). The combined organic layers were dried over MgSO<sub>4</sub>. Evaporation gave title compound (71 g, 85%) as a white solid.

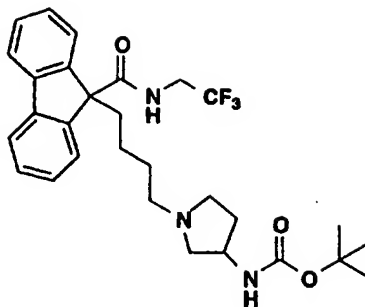
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B.



To a solution of Part A acid (60 g, 173 mmol) and DMF (100  $\mu$ L) in CH<sub>2</sub>Cl<sub>2</sub> (600 mL) under argon at 0°C was added oxalyl chloride (104 mL, 2.0M in CH<sub>2</sub>Cl<sub>2</sub>, 208 mmol) dropwise. The reaction was stirred at 0°C for 10 min, then warmed to RT and stirred for 1.5 h. The reaction was concentrated in vacuo to give the crude acid chloride as a yellow oil. To a suspension of 2,2,2-trifluoroethylamine hydrochloride (25.9 g, 191 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (500 mL) at 0°C under argon was added triethylamine (73 mL, 521 mmol) followed by dropwise addition of a solution of the crude acid chloride in CH<sub>2</sub>Cl<sub>2</sub> (15 mL). The reaction was stirred at 0°C for 1 h, diluted with CH<sub>2</sub>Cl<sub>2</sub> (500 mL), and washed with water (2 x 300 mL), 1N HCl (2 x 300 mL), saturated NaHCO<sub>3</sub> (2 x 300 mL), and brine (2 x 300 mL), then dried over MgSO<sub>4</sub>. Evaporation gave 80 g of a oil which was purified by flash chromatography on silica gel (2.5 kg). The crude product was loaded in a mixture of CH<sub>2</sub>Cl<sub>2</sub> and hexane, and eluted with a step gradient of 10% EtOAc/hexane (4L) to 15% EtOAc/hexane (2L) to 20% EtOAc/hexane (4L). Pure fractions were combined and evaporated to give title compound (52.5 g, 71%) as a white solid (mp 88-92°C).

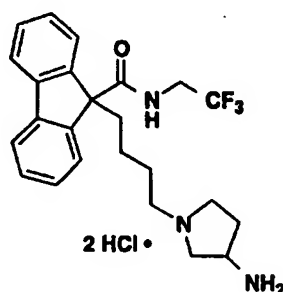
C.



- 5 A mixture of Part B compound (732 mg, 1.72 mmol), 3-(tert-butoxycarbonylamino)-pyrrolidine (383 mg, 2.06 mmol), and anhydrous potassium carbonate (356 mg, 2.58 mmol) in DMF (5 mL) was heated at 50°C under argon overnight (18 h),
- 10 cooled to RT, and the solvent removed under high vacuum. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and water (5 mL). The organic layer was washed with water (5 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated to give 1.2 g of an orange solid. The crude product was purified by flash chromatography on silica gel (70 g) eluting with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to provide title compound (673 mg, 74%) as a white foam.

20

D.



- To a solution of Part C compound (625 mg, 1.18 mmol) in dioxane (2 mL) was added 4N HCl in
- 25 dioxane (2 mL, 8 mmol). The clear solution was stirred at RT for 3 h, concentrated in vacuo, and

pumped under high vacuum overnight to give title compound (646 mg, >100%) as a white foamy solid.

E. 2-Phenoxybenzoic acid chloride

5 To a solution of 2-phenoxybenzoic acid (Aldrich) (500 mg, 2.33 mmol) and DMF (1 drop) in dichloromethane (10 mL) at RT was added dropwise a solution of oxalyl chloride in dichloromethane (2.0M, 1.28 mL, 2.56 mmol). Bubbling of escaping  
10 gasses continued for 10 min after addition. The reaction was stirred at RT for 60 min, then concentrated in vacuo to give title compound as an oil.

15 F. 9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,  
monohydrochloride

A solution of Part D compound (350 mg, 0.696 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was cooled to 0°C under argon. Triethylamine (385 µL, 2.78 mmol) was added, which gave a cloudy mixture. A  
20 solution of Part E acid chloride in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was added and the reaction mixture was stirred at 0°C for 10 min, diluted with CH<sub>2</sub>Cl<sub>2</sub> (2 mL),  
25 washed with water (2 mL) and saturated NaHCO<sub>3</sub> (2 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and then evaporated to give 450 mg of a gold-colored gum. The crude product was purified by flash chromatography on silica gel  
30 (50 g) eluting with 4% MeOH/CH<sub>2</sub>Cl<sub>2</sub> to provide 360 mg of the free amine as a white foam.

To a solution of the free amine in THF (3 mL) was added 1.1N HCl in Et<sub>2</sub>O (1.0 mL, 1.1 mmol). The reaction mixture was concentrated in vacuo,  
35 and the residue was triturated with Et<sub>2</sub>O. The resulting foam was dried in a vacuum oven (50°C,

0.2 torr) overnight to provide title compound (380 mg, 82%) as a foamy tan solid.

MS (ES, + ions) m/z 628 (M+H)

5 Anal. Calc'd for  $C_{37}H_{37}F_3N_3O_3 + 0.6H_2O$ :

C, 65.84; H, 5.70; N, 6.23; F, 8.44

Found: C, 66.20; H, 5.60; N, 6.13; F, 8.04.

### Example 2

10 9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

To a mixture of Example 1 compound (273 mg, 0.543 mmol) and triethylamine (300  $\mu$ L, 2.17 mmol) in  $CH_2Cl_2$  (2 mL) at 0°C under argon was added benzoyl chloride (70  $\mu$ L, 0.597 mmol). The reaction mixture was stirred at 0°C for 15 min, diluted with  $CH_2Cl_2$  (3 mL), washed with water (1 mL) and saturated  $NaHCO_3$  (2 mL), and then dried over  $Na_2SO_4$ . Evaporation of the filtrate gave a brown foam, which was purified by flash chromatography on silica gel (60 g) eluting with 3% MeOH/ $CH_2Cl_2$  to provide 196 mg of product as the free amine.

A portion of the desired product (176 mg) was dissolved in MeOH (2 mL) and a solution of 1.1N HCl/ $Et_2O$  (0.6 mL, 0.66 mmol) was added. The solution was concentrated in vacuo and the residue was triturated with  $Et_2O$  to give a foamy solid, which was pumped under high vacuum overnight to afford title compound (175 mg, 62%) as a foamy white solid.

MS (ES, + ions) m/z 536 (M+H)

Anal. Calc'd for  $C_{31}H_{33}Cl_3N_3O_2 + 0.4H_2O$ :

C, 64.28; H, 5.88; N, 7.25; Cl, 6.12;

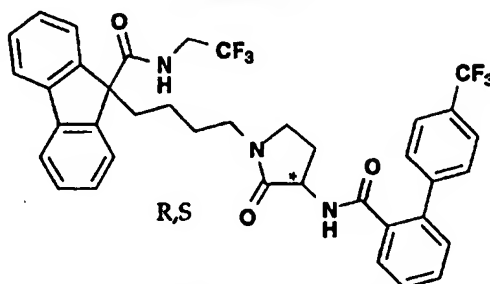
F, 9.84

Found: C, 64.27; H, 5.93; N, 7.29; Cl, 5.71;

5

F, 9.73.

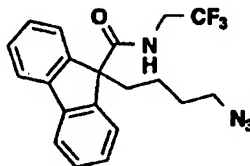
### Example 3



9-[4-[2-Oxo-3-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

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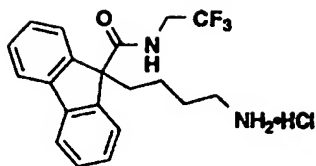
A.



A slurry of Example 1 Part B bromide (3.037 g, 7.12 mmol) and  $NaN_3$  (2.26 g, 34.7 mmol) in DMF (15 mL) was heated at 50°C for 3 hours and then at 95°C for 2 hours. The mixture was cooled to room temperature and partitioned between EtOAc and  $H_2O$ . The organic layer was washed successively with  $H_2O$ , 1 N HCl,  $H_2O$ , and brine, then dried ( $Na_2SO_4$ ), filtered and stripped to give a yellow oil which slowly solidified. Recrystallization from hexane afforded title azide compound (2.198 g) as a white solid. An additional 212 mg of material was obtained from the mother liquor to give a total of 2.41 g (87%) of title azide.

mp: 84-86°C.

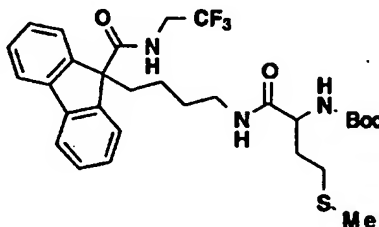
B.



A solution of Part A azide (2.253 g, 5.8  
 5 mmol) in MeOH (40 mL) was hydrogenated (balloon)  
 over palladium (10% Pd on carbon, 250 mg) at room  
 temperature for 1 hour. The mixture was filtered  
 through Celite and the filtrate was stripped, re-  
 dissolved in MeOH, and treated with 4 N HCl in  
 10 dioxane. Trituration with Et<sub>2</sub>O followed by  
 collection of the precipitate and drying in vacuo  
 afforded title compound (2.090 g, 90%) as a  
 grayish white solid.  
 mp: 200-202°C.

15

C.

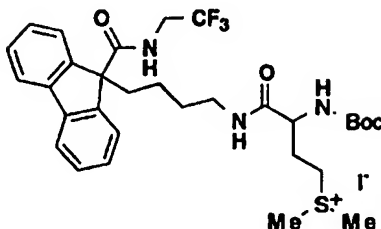


A solid mixture of Part B compound (2.048  
 20 g, 5.1 mmol), N-Boc-D,L-methionine (1.280 g, 5.1  
 mmol), and HOBT·xH<sub>2</sub>O (693 mg) was slurried in  
 CH<sub>2</sub>Cl<sub>2</sub> and subsequently treated with N-methyl-  
 morpholine (0.9 mL, 828 mg, 8.2 mmol) followed by  
 ethyl-3-(3-dimethylamino)propyl carbodiimide ·HCl  
 25 salt (EDAC) (1.083 g, 5.6 mmol). After stirring at  
 room temperature for 18 hours, the homogeneous  
 mixture was partitioned between EtOAc/Et<sub>2</sub>O and 1 N  
 HCl. The organic layer was washed with H<sub>2</sub>O, 50%  
 saturated NaHCO<sub>3</sub>, and brine, then dried (Na<sub>2</sub>SO<sub>4</sub>),  
 30 filtered and stripped to give racemic title  
 compound (2.972 g, 98%) as a foam.



TLC:  $R_f$  0.44 (6/4-EtOAc/hexanes).

D.

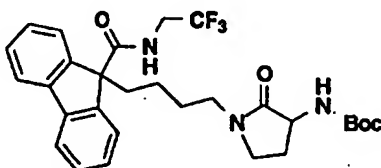


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Part C compound (2.902 g, 4.88 mmol) was dissolved in  $\text{CH}_3\text{I}$  (35 mL) and stirred at room temperature for 2 days. The solvent was stripped, then triturated and stripped from hexane twice to give crude title compound (3.74 g, 104% of theory) as a pale yellow solid which was used directly in the next reaction without further purification.

10

E.



15

A solution of Part D sulfonium salt (3.069 g, 4.17 mmol) in DMF (20 mL) and  $\text{CH}_2\text{Cl}_2$  (22 mL) at  $0^\circ\text{C}$  was treated all at once with solid NaH (60% in mineral oil, 400 mg, 240 mg pure, 10.0 mmol). After stirring at  $0^\circ\text{C}$  for 1.5 hours and at room temperature for 1.5 hours, the mixture was quenched with 0.5 N HCl and extracted with EtOAc. The EtOAc extract was washed twice with  $\text{H}_2\text{O}$ , once with saturated  $\text{NaHCO}_3$ , and once with brine, then dried ( $\text{Na}_2\text{SO}_4$ ), filtered and stripped. Flash chromatography (Merck  $\text{SiO}_2$ , 7/3-EtOAc/hexanes) afforded title compound (1.774 g, 78%) as a white foam.

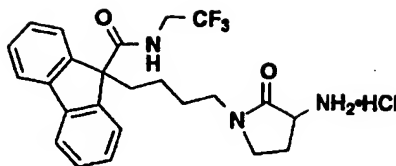
20

25

30

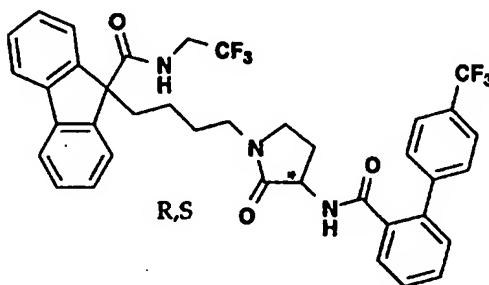
TLC:  $R_f$  0.21 (6/4-EtOAc/hexane).

F.



A solution of Part E compound (1.752 g, 3.2  
 5 mmol) in 1,4-dioxane (8 mL) was treated with 4 N  
 HCl in 1,4-dioxane (5 mL). After 5 hours, the  
 solvent was stripped and the residue was  
 azeotroped twice from CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O and triturated  
 from Et<sub>2</sub>O/hexane. The solid was collected by  
 10 filtration and dried in vacuo to give title  
 compound (1.576 g, 102% of theory) as a white  
 solid.

G.



15

A solid mixture of Part F compound (250 mg,  
 0.52 mmol), 4'-(trifluoromethyl)-2-biphenylcar-  
 boxylic acid (145 mg, 0.54 mmol), and HOBT·xH<sub>2</sub>O (70  
 20 mg) was slurried in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and subsequently  
 treated with N-methyl morpholine (86 uL, 79 mg,  
 0.78 mmol) followed by EDAC (111 mg, 0.58 mmol).  
 After stirring at room temperature for 18 hours,  
 the mixture was partitioned between EtOAc and 1 N  
 25 HCl. The EtOAc extract was washed successively  
 with H<sub>2</sub>O, saturated NaHCO<sub>3</sub> and brine, then dried  
 (Na<sub>2</sub>SO<sub>4</sub>), filtered and stripped. Flash chromato-  
 graphy (Merck SiO<sub>2</sub>, 8/2-EtOAc/hexanes) afforded  
 title compound (310 mg, 86%) as a white foam.

TLC:  $R_f$  0.21 (8/2-EtOAc/hexanes)

MS:  $(M+H)^+$  @ 694;  $(M-H)^-$  692;  $(M+NH_4)^+$  711

HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted

5 with 0% to 100% B, 30 minute gradient, (A = 90% H<sub>2</sub>O-10% MeOH-0.2% H<sub>3</sub>PO<sub>4</sub> and B = 10% H<sub>2</sub>O-90% MeOH-0.2% H<sub>3</sub>PO<sub>4</sub>) flow rate at 1.5 ml/min detecting at 220 nm;  $t_R$  = 30.98 min (98.1%).

Microanalysis Calc'd for C<sub>38</sub>H<sub>33</sub>F<sub>6</sub>N<sub>3</sub>O<sub>3</sub> + 0.13CH<sub>2</sub>Cl<sub>2</sub>:

10 C, 64.96; H, 4.76; N, 5.96; F, 16.17;

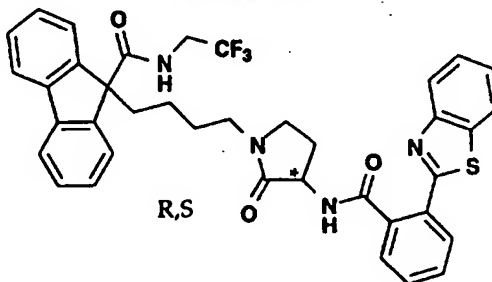
Cl, 1.35

Found: C, 64.86; H, 4.80; N, 5.89; F, 16.22;

Cl 1.34.

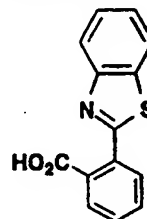
15

#### Example 4



9-[4-{3-[[2-(2-Benzothiazolyl)benzoyl]amino]-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A slurry of Example 3 Part F amine



20 hydrochloride (200 mg, 0.415 mmol), (98 mg, 0.38 mmol), and HOBT·xH<sub>2</sub>O (56 mg) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was treated successively with N-methyl morpholine (70  $\mu$ L, 65 mg, 0.65 mmol) and EDAC (89 mg, 0.46 mmol) at room temperature. After 18

25 hours, the mixture was partitioned between EtOAc and saturated NaHCO<sub>3</sub>. The EtOAc extract was washed successively with H<sub>2</sub>O, 1 N HCl, and brine, then

dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and stripped repeatedly from  $\text{CH}_2\text{Cl}_2$  to give title compound (249 mg, 95%) as a white foam.

TLC:  $R_f$  0.19 (EtOAc)

5 MS:  $(\text{M}+\text{H})^+$  @ 683;  $(\text{M}-\text{H})^-$  681

HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90%  $\text{H}_2\text{O}$ -10% MeOH-0.2%  $\text{H}_3\text{PO}_4$  and B = 10%  $\text{H}_2\text{O}$ -90% MeOH-0.2%  $\text{H}_3\text{PO}_4$ ) flow rate at 1.5 ml/min detecting at

10 254 nm;  $t_R$  = 18.9 min (96.6%).

Microanalysis Calc'd for  $\text{C}_{38}\text{H}_{33}\text{F}_3\text{N}_4\text{O}_3\text{S}+0.09 \text{CH}_2\text{Cl}_2$ :

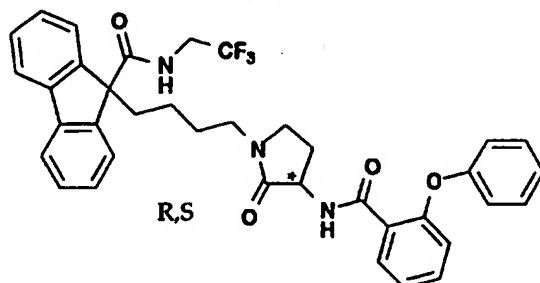
C, 66.27; H, 4.84; N, 8.12; F, 8.26;

S, 4.64; Cl, 0.92

Found: C, 65.92; H, 3.92; N, 7.81; F, 7.98;

15 S, 4.56; Cl, 0.70.

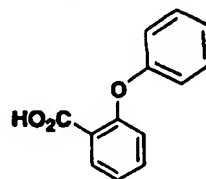
#### Example 5



9-[4-[2-Oxo-3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

20

A slurry of Example 3 Part F amine



hydrochloride (200 mg, 0.415 mmol),

(85 mg, 0.40 mmol), and HOBT·xH<sub>2</sub>O (56 mg) in  $\text{CH}_2\text{Cl}_2$

(7 mL) was treated successively with N-methyl

25 morpholine (70  $\mu\text{L}$ , 65 mg, 0.65 mmol) and EDAC (89

mg, 0.46 mmol) at room temperature. After 22

hours, the mixture was partitioned between EtOAc

and saturated  $\text{NaHCO}_3$ . The EtOAc extract was washed

successively with H<sub>2</sub>O, 1 N HCl, and brine, then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and stripped repeatedly from CH<sub>2</sub>Cl<sub>2</sub> to give title compound (224 mg, 87%) as a white foam.

5

TLC: R<sub>f</sub> 0.46 (EtOAc)

MS: (M+H)<sup>+</sup> @ 642; (M-H)<sup>-</sup> 640

HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% H<sub>2</sub>O-10% MeOH-0.2% H<sub>3</sub>PO<sub>4</sub> and B = 10% H<sub>2</sub>O-90% MeOH-0.2% H<sub>3</sub>PO<sub>4</sub>) flow rate at 1.5 ml/min detecting at 254 nm; t<sub>R</sub> = 19.7 min (100%).

10

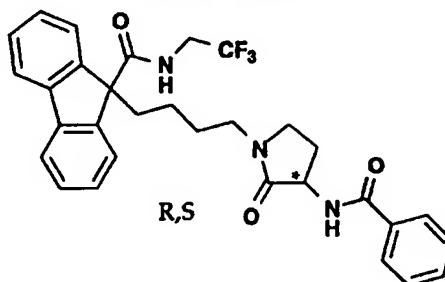
Microanalysis Calc'd for C<sub>37</sub>H<sub>34</sub>F<sub>3</sub>N<sub>3</sub>O<sub>4</sub>:

C, 69.26; H, 5.34; N, 6.55; F, 8.88

15

Found: C, 68.92; H, 5.25; N, 6.42; F, 8.70.

#### Example 6



9-[4-[3-(Benzoylamino)-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

20

A solution of Example 3 Part F amine hydrochloride (200 mg, 0.415 mmol) and triethylamine (TEA) (200  $\mu$ L, 145 mg, 1.43 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) at 0°C was treated with benzoyl chloride (48  $\mu$ L, 58 mg, 0.41 mmol). After 45 minutes, the mixture was quenched with saturated NaHCO<sub>3</sub> and extracted with EtOAc. The EtOAc extract was washed successively with H<sub>2</sub>O, 1 N HCl, H<sub>2</sub>O, and brine, then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and stripped to give title compound (231 mg, 98%) as a white foam.

30

TLC:  $R_f$  0.35 (EtOAc)

MS:  $(M+H)^+$  @ 550;  $(M-H)^-$  548

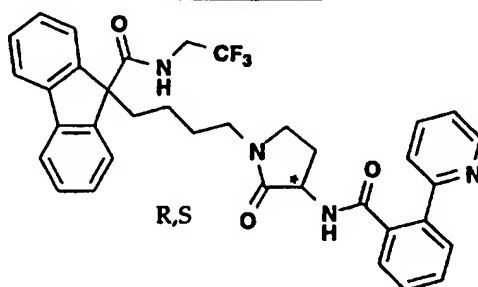
HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% H<sub>2</sub>O-10% MeOH-0.2% H<sub>3</sub>PO<sub>4</sub> and B = 10% H<sub>2</sub>O-90% MeOH-0.2% H<sub>3</sub>PO<sub>4</sub>) flow rate at 1.5 ml/min detecting at 254 nm;  $t_R$  = 16.2 min (96.7%).

Microanalysis Calc'd for C<sub>31</sub>H<sub>30</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> + 0.2EtOAc:

C, 67.34; H, 5.62; N, 7.41; F, 9.59

10 Found: C, 67.15; H, 5.55; N, 7.13; F, 9.73.

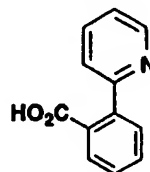
### Example 7



9-[4-[2-Oxo-3-[[2-(2-pyridinyl)benzoyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

15

A slurry of Example 3 Part F amine



hydrochloride (202 mg, 0.419 mmol), (88 mg, 0.44 mmol), and 1-hydroxy-7-azabenzotriazole (HOAT) (55 mg) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was treated

20 successively with N-methyl morpholine (56  $\mu$ L, 52 mg, 0.51 mmol) and EDAC (87.5 mg, 0.46 mmol) at room temperature. After 18 hours, the mixture was partitioned between EtOAc and saturated NaHCO<sub>3</sub>. The EtOAc extract was washed successively with H<sub>2</sub>O  
25 and brine, then dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and stripped. The residue was flash chromatographed (Merck SiO<sub>2</sub>, 5/95-MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluant) to give title compound (259 mg, 94%) as a white foam.

TLC:  $R_f$  0.47 (1/9-MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

MS: (M+H)<sup>+</sup> @ 627

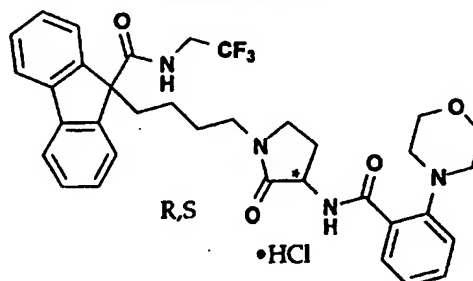
HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted  
 5 with 40% to 100% B, 20 minute gradient, (A = 90%  
 H<sub>2</sub>O-10% MeOH-0.2% H<sub>3</sub>PO<sub>4</sub> and B = 10% H<sub>2</sub>O-90% MeOH-  
 0.2% H<sub>3</sub>PO<sub>4</sub>) flow rate at 1.5 ml/min detecting at  
 254 nm;  $t_R$  = 11.6 min (98.9%).

Microanalysis Calc'd for C<sub>36</sub>H<sub>33</sub>F<sub>3</sub>N<sub>4</sub>O<sub>3</sub>+0.35 CH<sub>2</sub>Cl<sub>2</sub>:

10 C, 66.51; H, 5.18; N, 8.54; F, 8.68

Found: C, 66.88; H, 5.07; N, 8.36; F, 7.91.

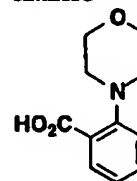
### Example 8



15

9-[4-[3-[[2-(4-Morpholinyl)benzoyl]amino]-2-oxo-1-pyrrolidiny]butyl]-  
 N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

A slurry of Example 3 Part F amine



hydrochloride (200 mg, 0.415 mmol), (111  
 mg, 0.53 mmol), and HOAT (53 mg) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL)  
 20 was treated successively with N-methyl morpholine  
 (100  $\mu$ L, 93 mg, 0.91 mmol) and EDAC (90 mg, 0.47  
 mmol) at room temperature. After 20 hours, the  
 mixture was partitioned between EtOAc and  
 saturated NaHCO<sub>3</sub>. The EtOAc extract was washed  
 25 successively with H<sub>2</sub>O and brine, then dried  
 (Na<sub>2</sub>SO<sub>4</sub>), filtered, and stripped to give an oil.  
 The residue was flash chromatographed (Merck SiO<sub>2</sub>,  
 5/95-MeOH/CH<sub>2</sub>Cl<sub>2</sub> as eluant) to give the free base

of title compound (141 mg, 53%) as pale yellow oil. The oil was dissolved in 1,4-dioxane (2 mL), treated with 4 N HCl in 1,4-dioxane (150  $\mu$ L) and added via cannula to rapidly swirling Et<sub>2</sub>O (30 mL).

- 5 The precipitate was collected by filtration and dried in vacuo to give title compound (101 mg, 35% from Example 3 Part F compound) as a pink solid.

TLC: R<sub>f</sub> 0.64 (1/9-MeOH/CH<sub>2</sub>Cl<sub>2</sub>)

- 10 MS: (M+H)<sup>+</sup> @ 635

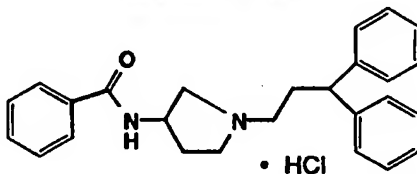
HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% H<sub>2</sub>O-10% MeOH-0.2% H<sub>3</sub>PO<sub>4</sub> and B = 10% H<sub>2</sub>O-90% MeOH-0.2% H<sub>3</sub>PO<sub>4</sub>) flow rate at 1.5 ml/min detecting at

- 15 254 nm; t<sub>R</sub> = 16.9 min (98.7%).

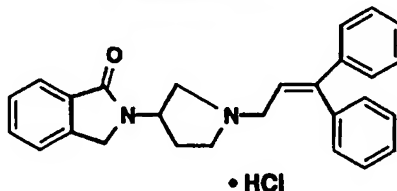
The following Examples represent preferred embodiments of the invention and may be prepared employing procedures described herein.

20

Example 8A

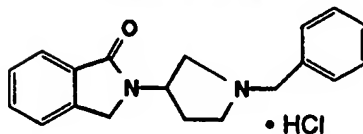


Example 8B

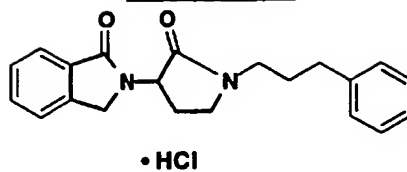


25

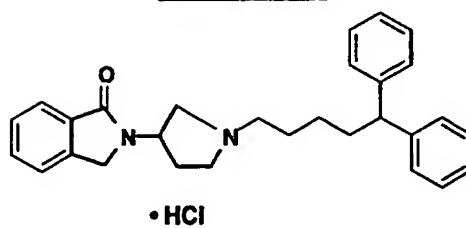
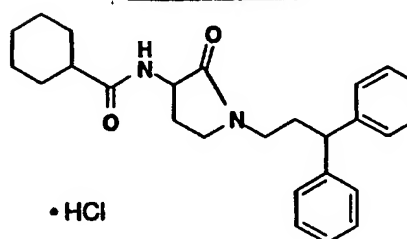
Example 8C



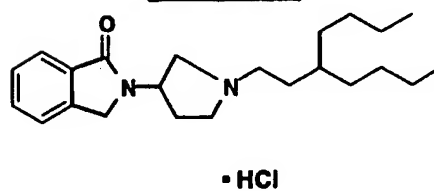
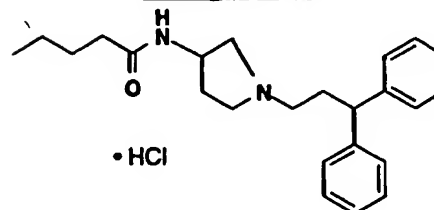


Example 8D

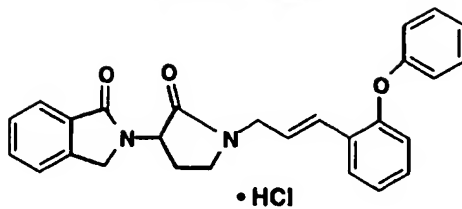
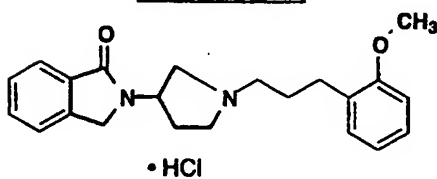
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Example 8EExample 8F

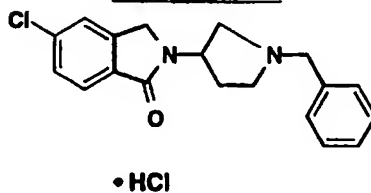
10

Example 9Example 10

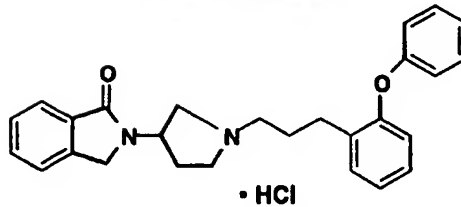
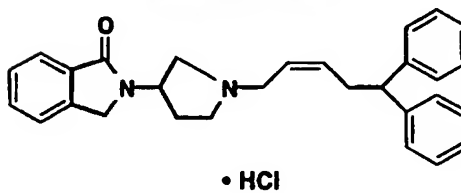
15

Example 11Example 12

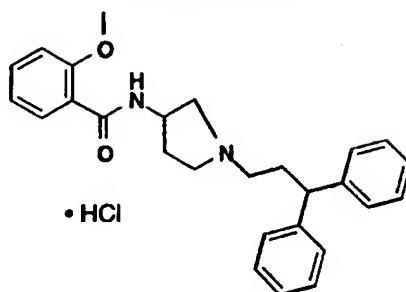
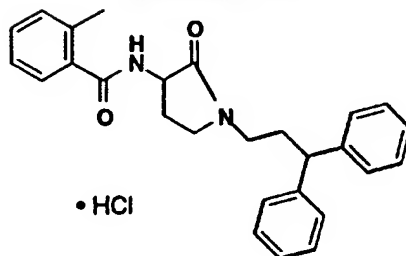
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Example 13

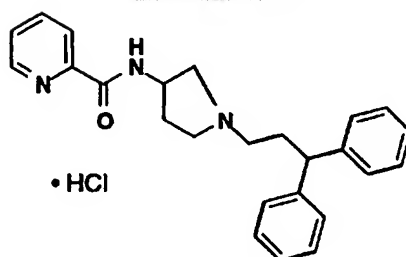
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Example 14Example 15

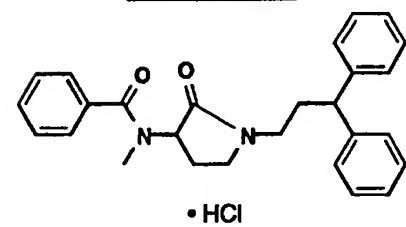
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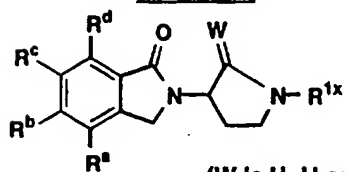
Example 16Example 17

5

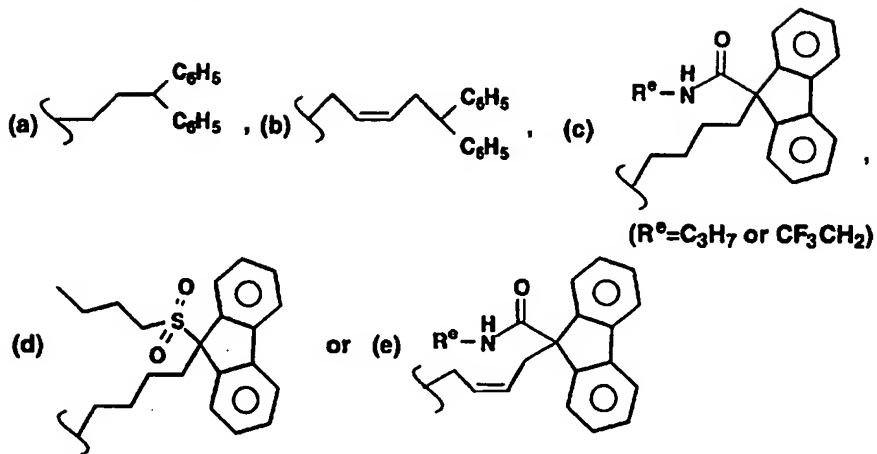
Example 18

10

Example 19

Examples 20 to 202Table A

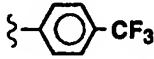
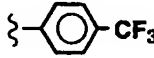

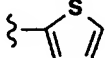
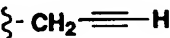


(W is H, H or O)

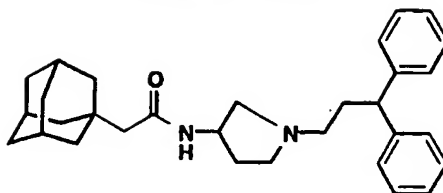
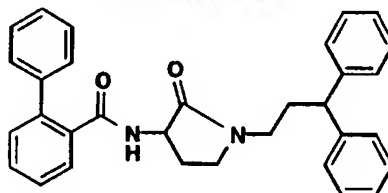
where  $R^{1x}$  is

5

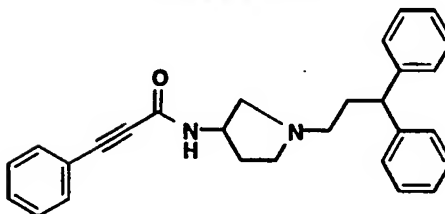
	$R^a$	$R^b$	$R^c$	$R^d$
10	H	H	H	F
	H	H	H	$\zeta-O$
	H	H	H	
15	H	H	F	Cl
	H	H	$CF_3$	H
	H	$OCH_3$	H	H
	H	H	H	
	$\zeta-CH_2$			
	$\zeta-OCH_2$			
20	H	H	H	H
	F	Cl	H	H
	H	H		H
	H	H	H	$\zeta-S$
	H	H	H	

Table A (continued)

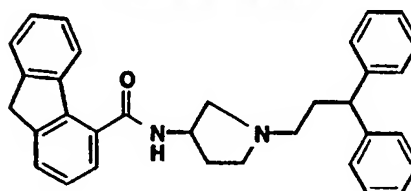
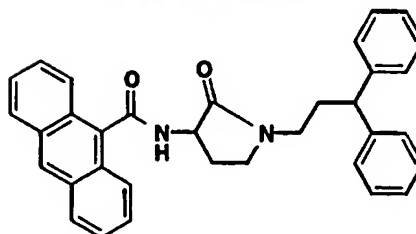
	R <sup>a</sup>	R <sup>b</sup>	R <sup>c</sup>	R <sup>d</sup>
5		H	H	
	H	H	H	H
	H	H	Cl	
	H	H	H	H
	H	H	H	H
10	H	H	H	Cl
	H	H	CH <sub>3</sub>	H
	H	CH <sub>3</sub>	H	
	SCH <sub>3</sub>	H	H	H
	H	H	OCH <sub>3</sub>	H
15	H	H	H	SCH <sub>3</sub>
	H	H	H	H
	H	H	H	
	H	H	H	H
	H		H	H
	H	H	H	
20				

Example 203Example 204

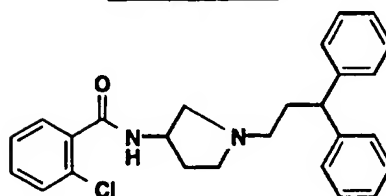
5

Example 205

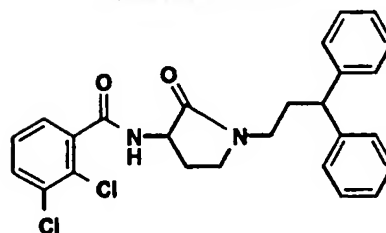
10

Example 206Example 207

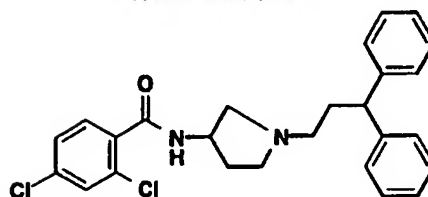
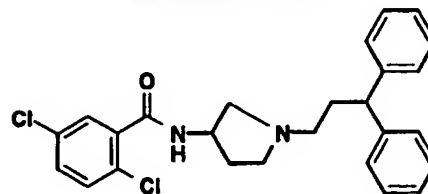
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Example 208Example 209

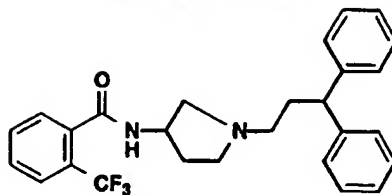
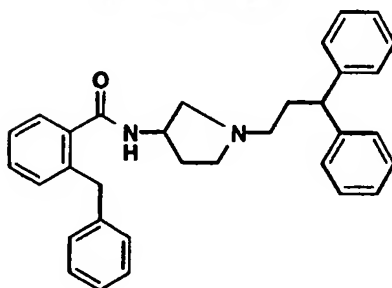
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Example 210

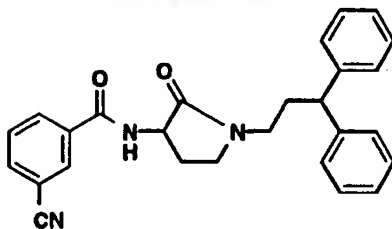
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Example 211Example 212

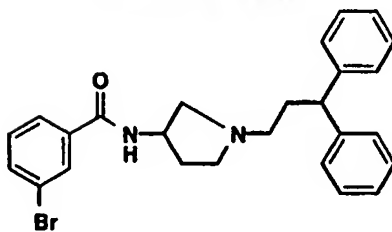
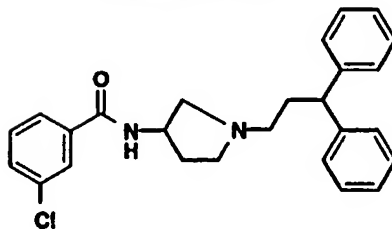
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Example 213Example 214

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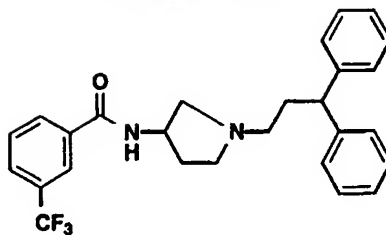
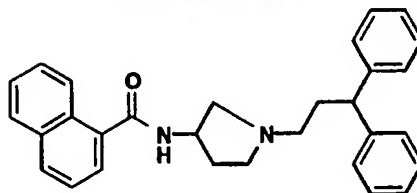
Example 215

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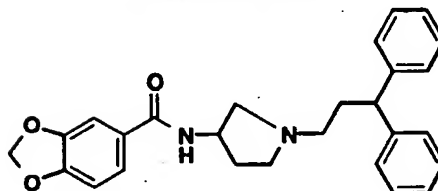
Example 216Example 217

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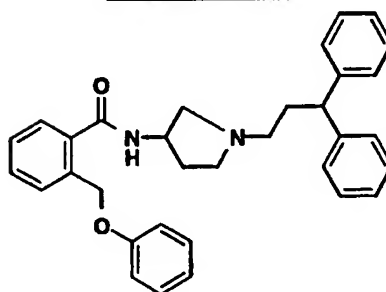
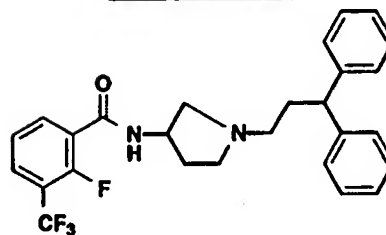


Example 218Example 219

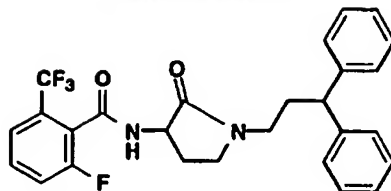
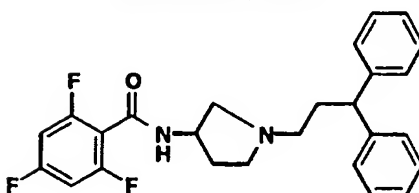
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Example 220

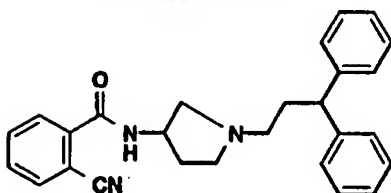
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Example 221Example 222

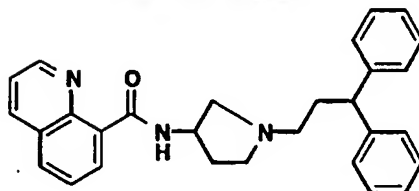
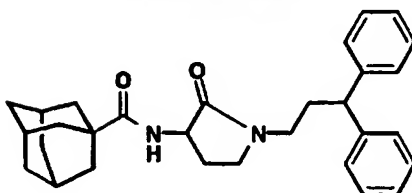
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Example 223Example 224

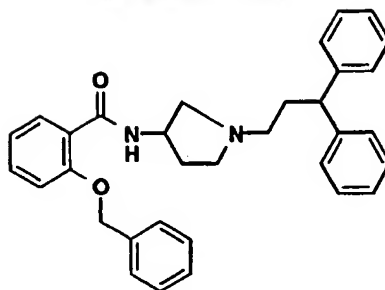
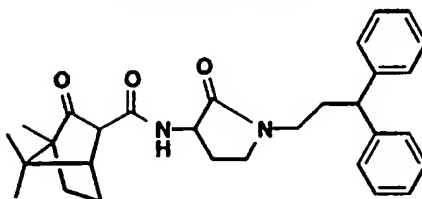
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Example 225

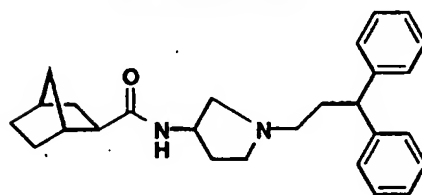
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Example 226Example 227

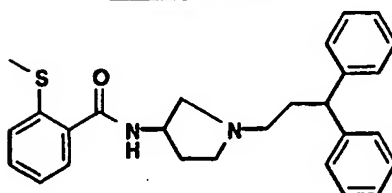
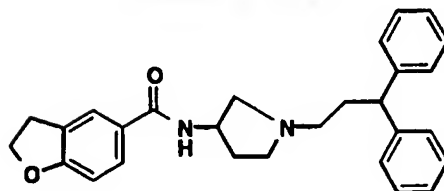
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Example 228Example 229

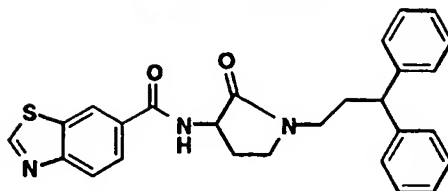
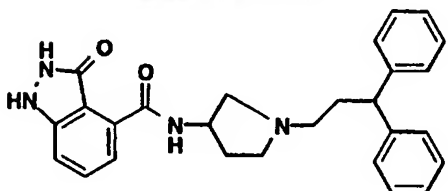
5

Example 230

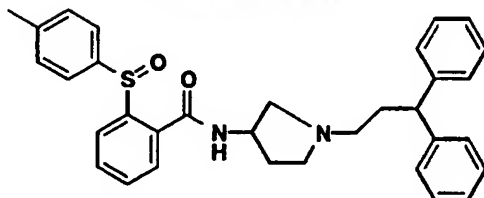
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Example 231Example 232

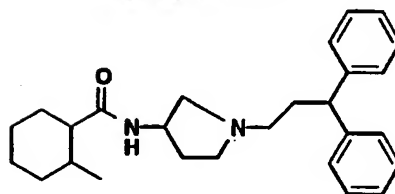
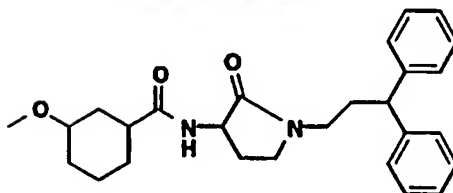
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Example 233Example 234

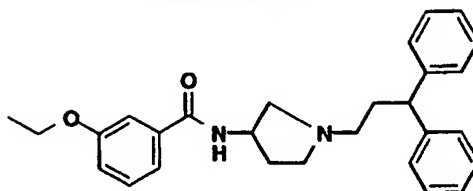
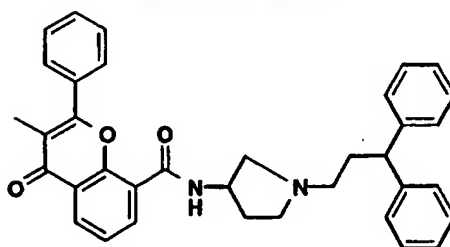
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Example 235

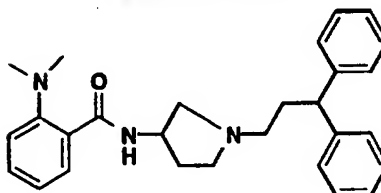
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Example 236Example 237

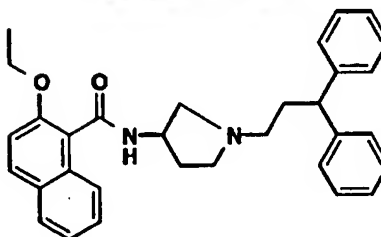
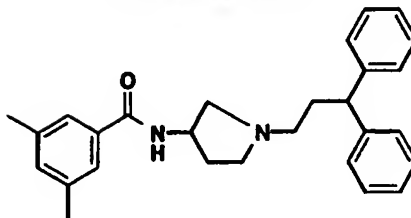
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Example 238Example 239

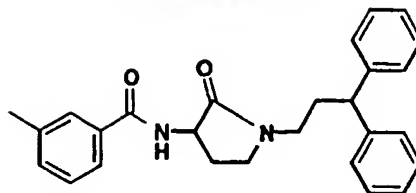
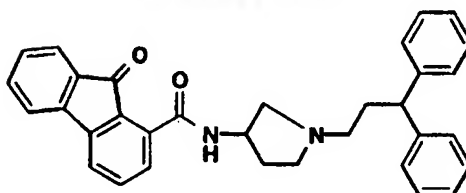
5

Example 240

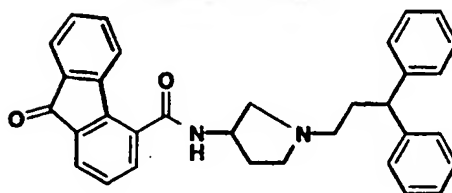
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Example 241Example 242

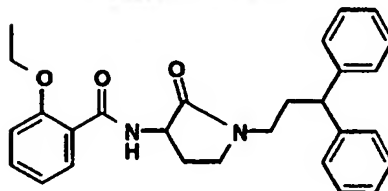
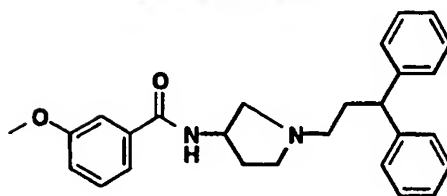
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Example 243Example 244

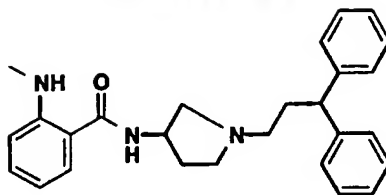
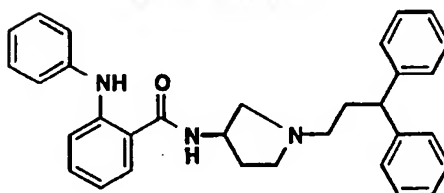
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Example 245

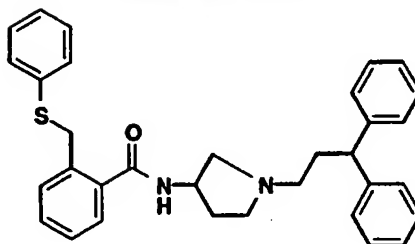
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Example 246Example 247

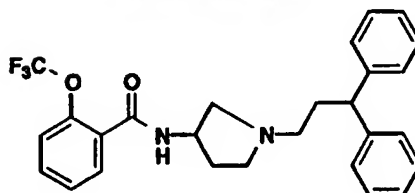
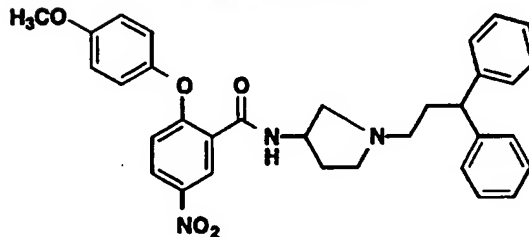
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Example 248Example 249

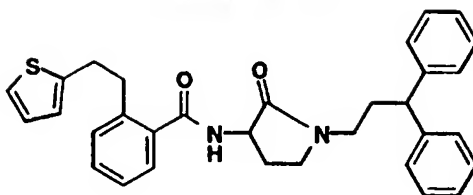
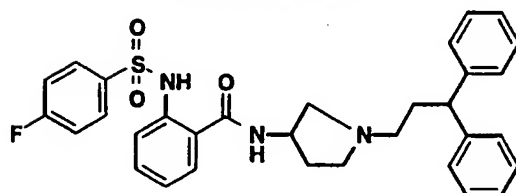
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Example 250

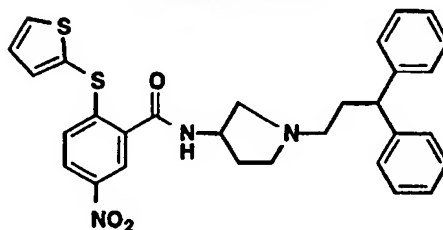
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Example 251Example 252

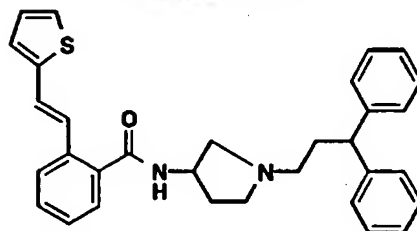
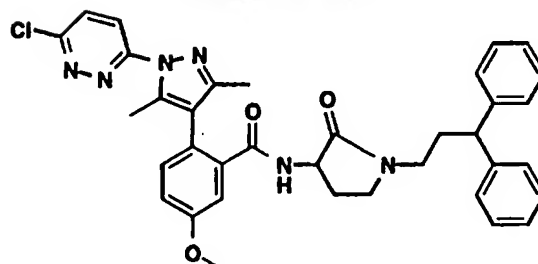
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Example 253Example 254

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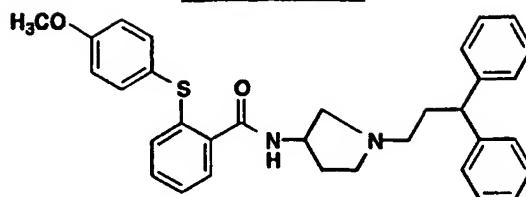
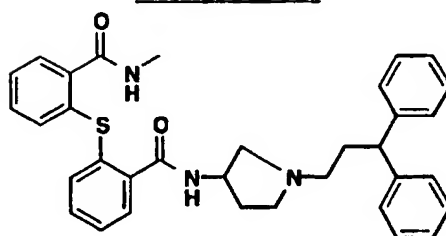
Example 255

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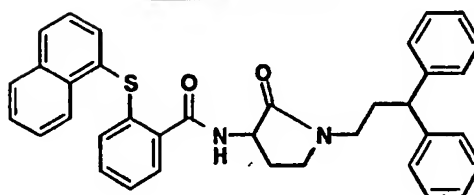
Example 256Example 257

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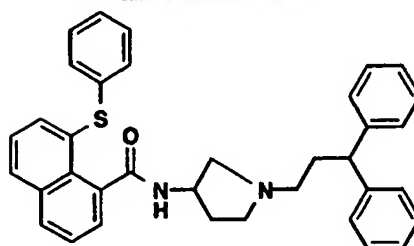
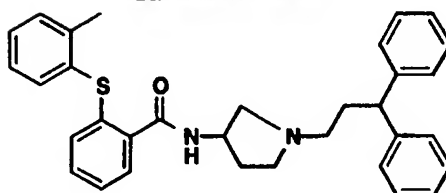


Example 258Example 259

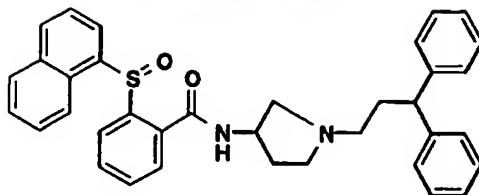
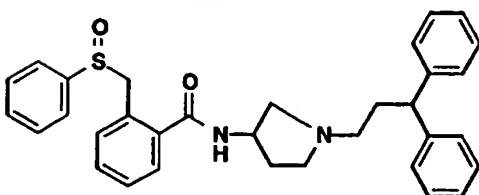
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Example 260

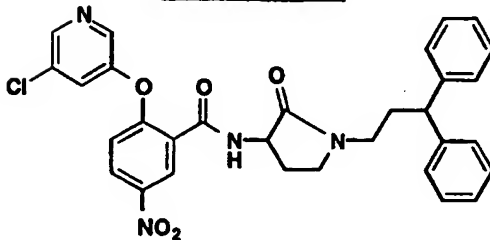
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Example 261Example 262

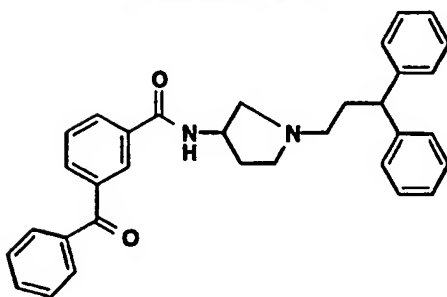
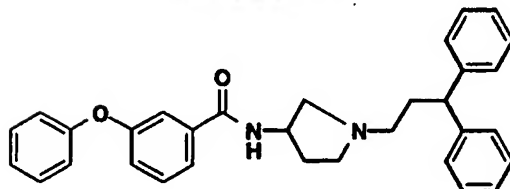
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Example 263Example 264

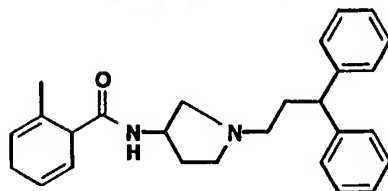
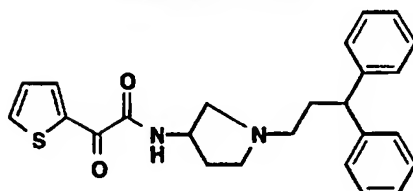
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Example 265

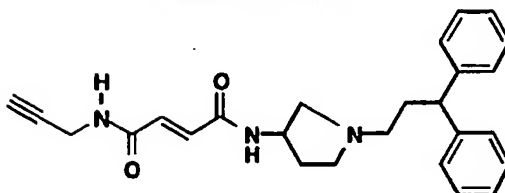
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Example 266Example 267

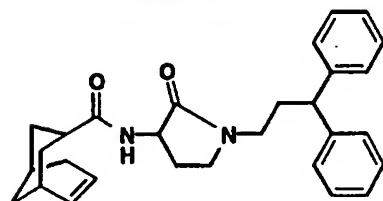
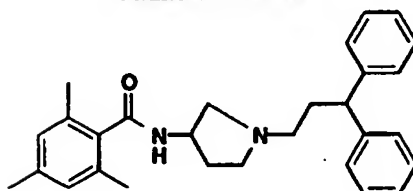
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Example 268Example 269

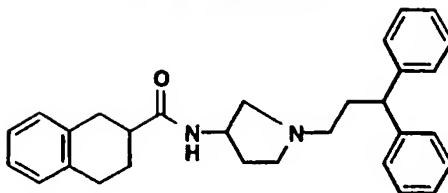
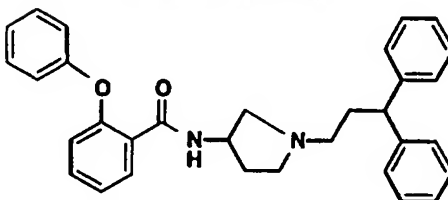
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Example 270

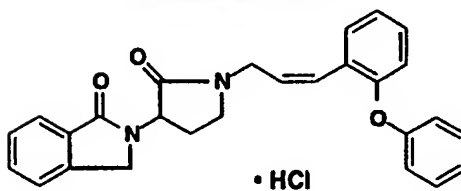
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Example 271Example 272

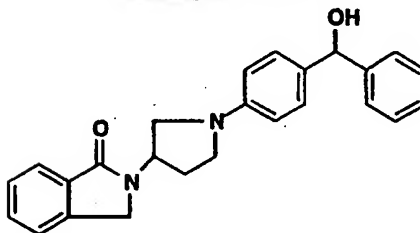
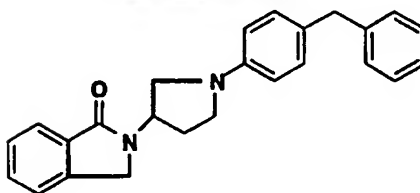
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Example 273Example 274

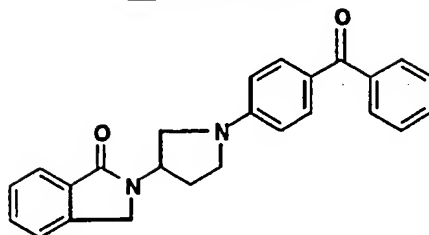
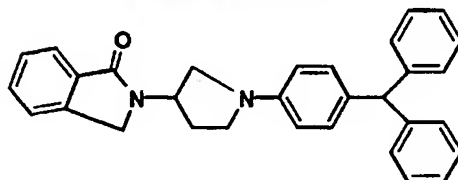
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Example 275

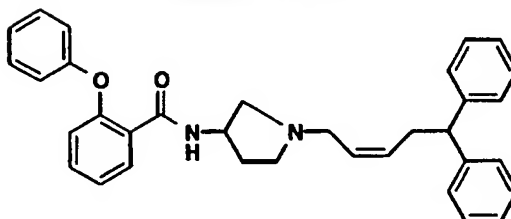
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Example 276Example 277

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Example 278Example 279

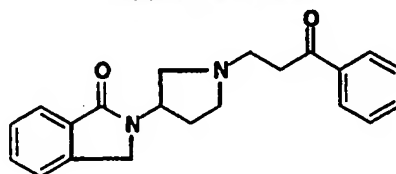
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Example 280

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Example 281

(Z)-N-[1-(5,5-Diphenyl-2-pentenyl)-3-pyrrolidinyl]-2-phenoxybenzamide

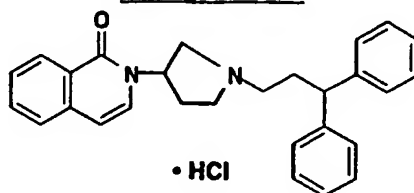
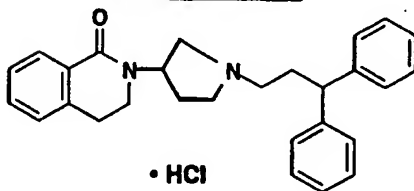
Example 282

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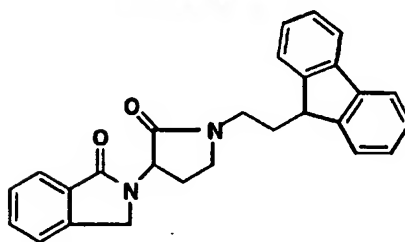
**Example 283**

2,3-Dihydro-2-[1-[3-phenyl-3-(4-propylphenyl)-  
propyl]-3-pyrrolidinyl]-1H-isoindol-1-one,  
monohydrochloride

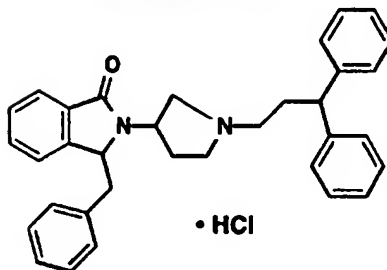
5

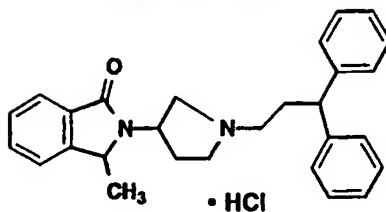
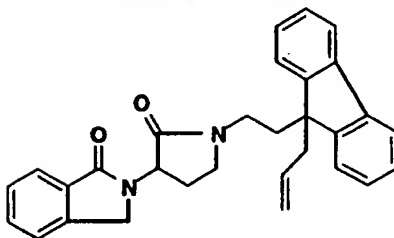
**Example 284****Example 285**

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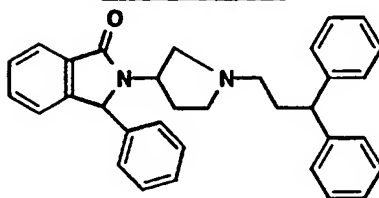
**Example 286**

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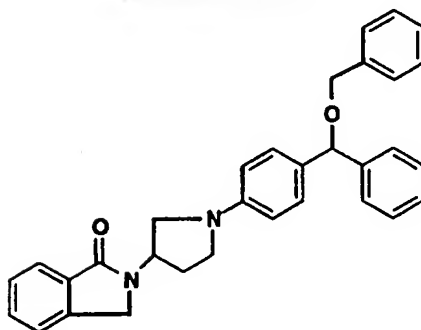
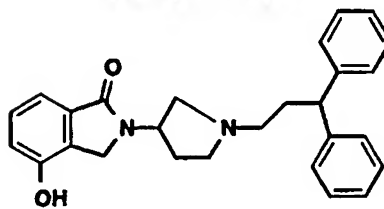
**Example 287**

Example 288Example 289

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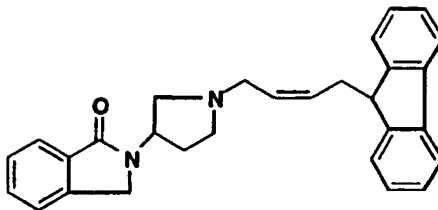
Example 290

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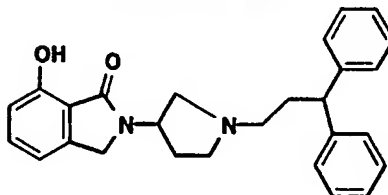
Example 291Example 292

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### Example 293

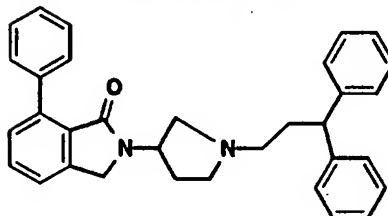


### Example 294



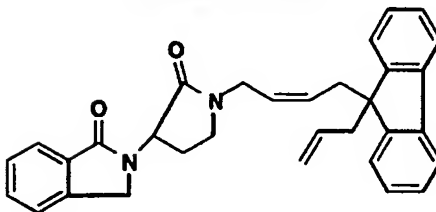
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### Example 295

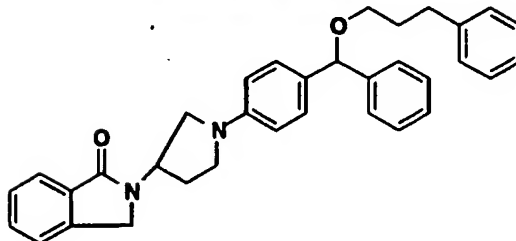


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### Example 296

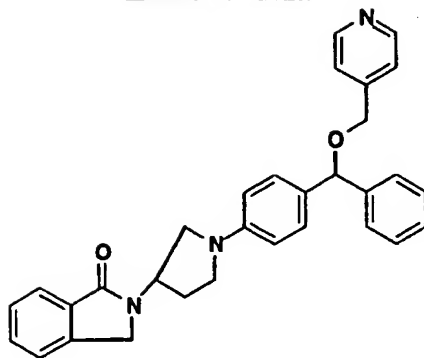
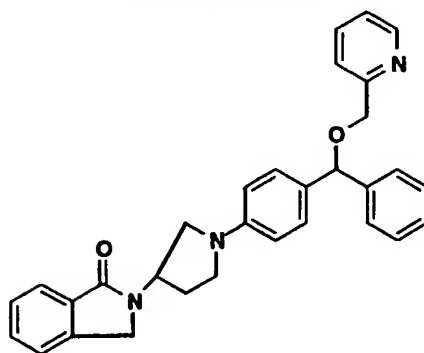


### **Example 297**

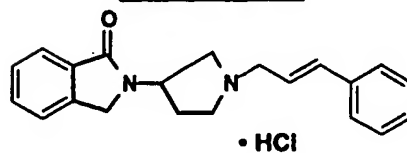


15

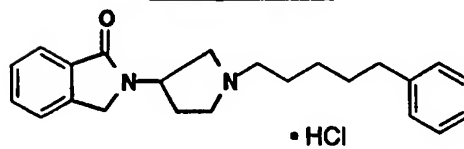
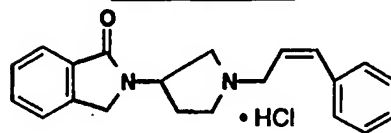


Example 298Example 299

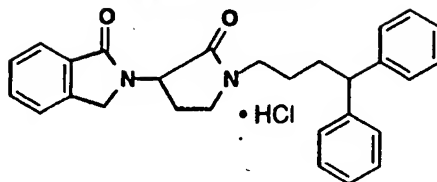
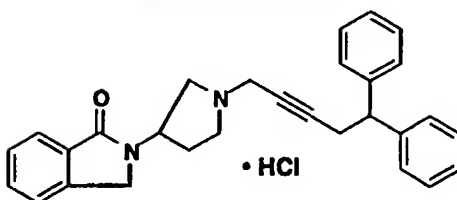
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Example 300

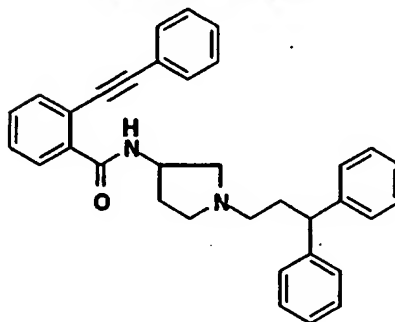
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Example 301Example 302

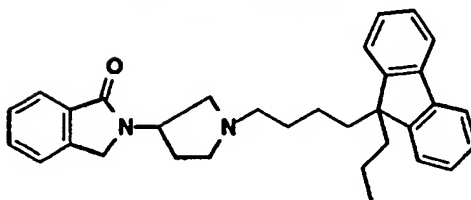
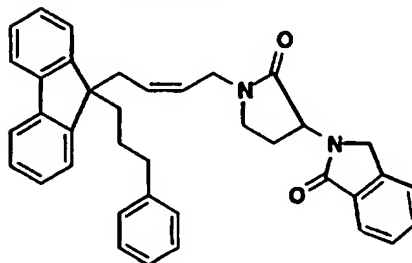
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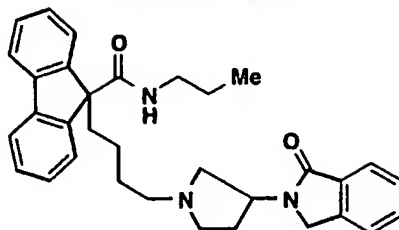
Example 303Example 304

5

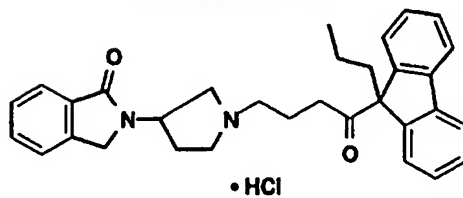
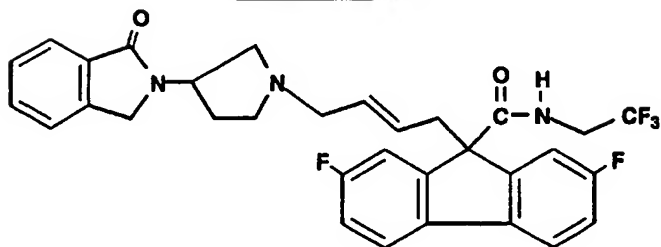
Example 305

10

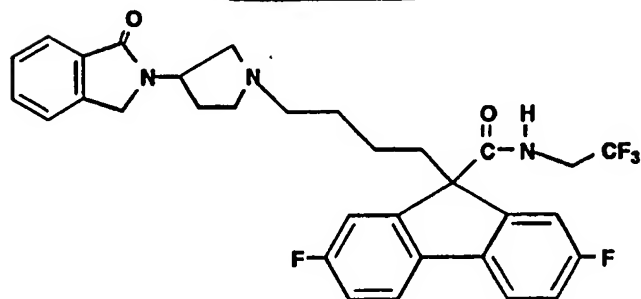
Example 306Example 307

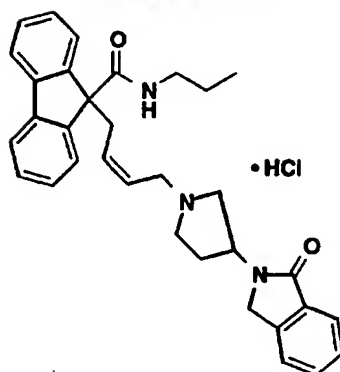
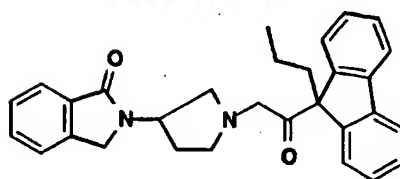
Example 308

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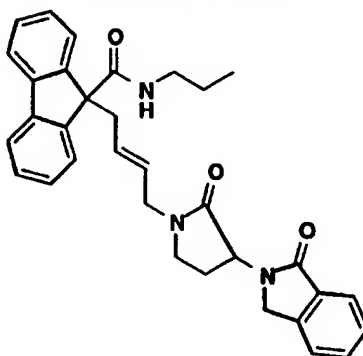
Example 309Example 310

10

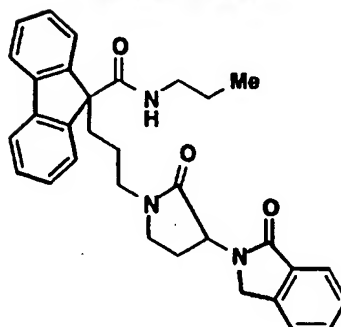
Example 311

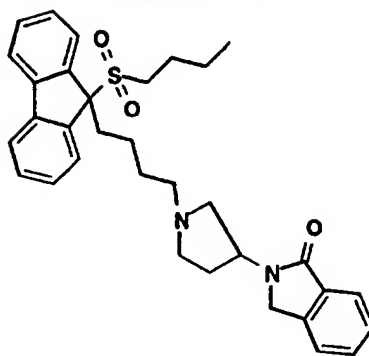
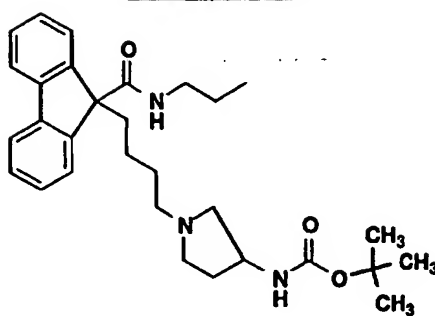
Example 312Example 313

5

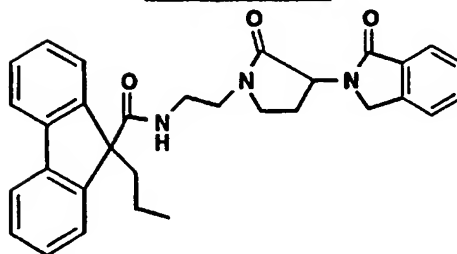
Example 314

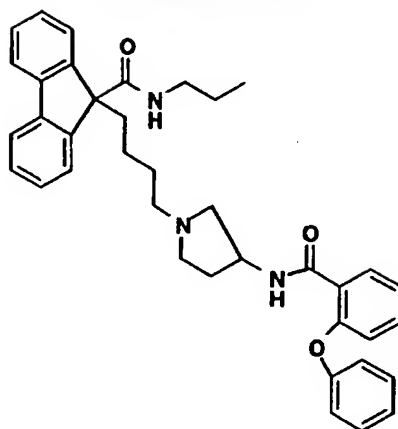
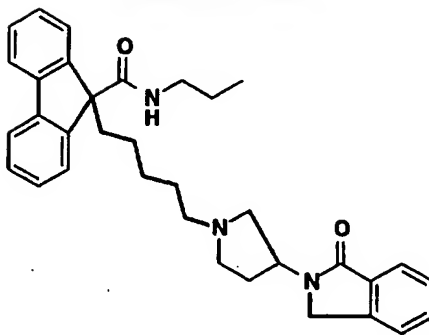
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Example 315

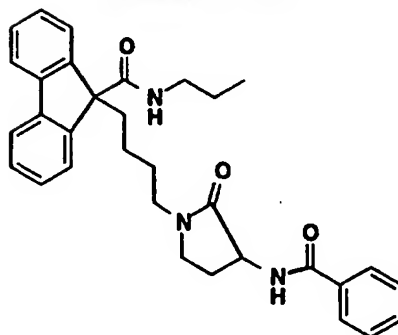
Example 316Example 317

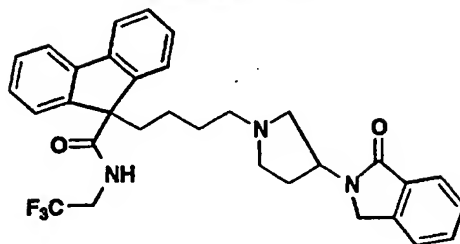
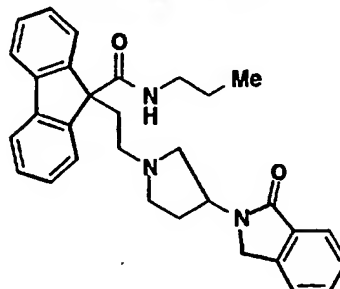
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Example 318

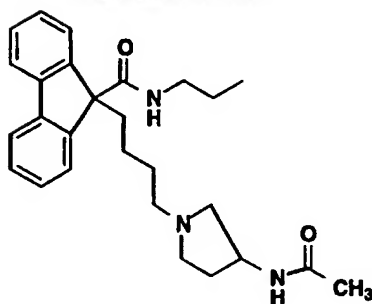
Example 319Example 320

5

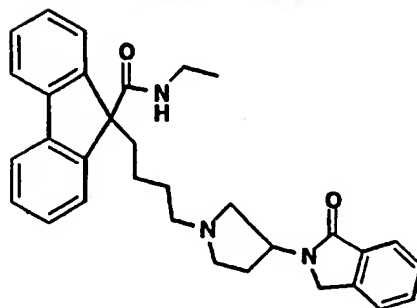
Example 321

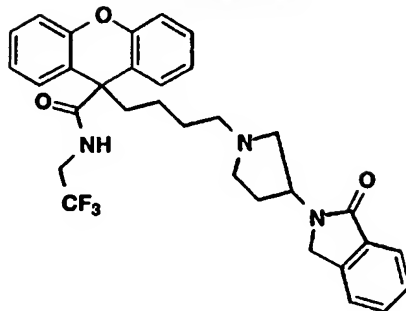
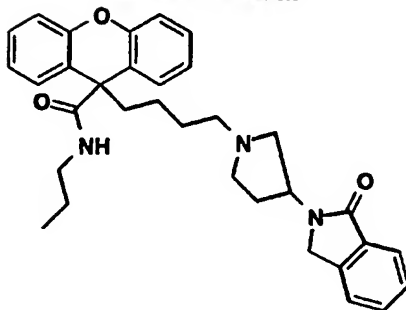
Example 322Example 323

5

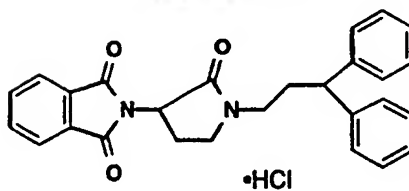
Example 324

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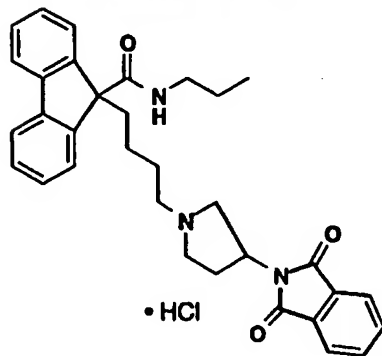
Example 325

Example 326Example 327

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Example 328

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Example 329



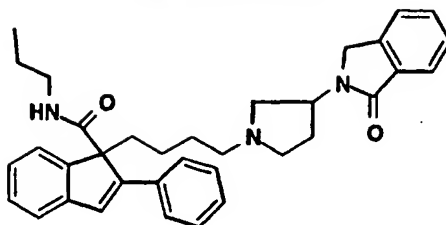
CCNC(=O)C1(C2=CC=CC=C2C3=CC=CC=C3N=C2)CCCCN4CC[C@H](C4)N5C(=O)c6ccccc65CCCC(O)(Cc1ccc2ccccc2c1)CCN3CCCN3C4Cc5ccccc5C(=O)N4

5

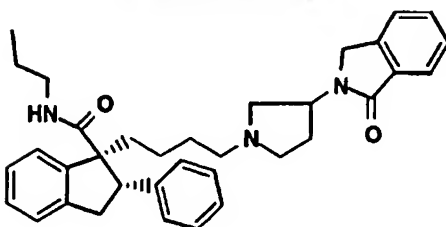
CC(C)C1(c2ccccc2-c3ccccc13)SCCCNC(=O)C1CCN1C(=O)c2ccccc2

10

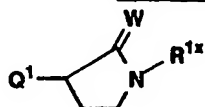
CC(C)(S(=O)(=O)CCCN1CCCN1C2=CC=C3C(=O)NCC3=C2)c4c5ccccc45CCNC(=O)C1CCC2c3ccccc3C1CCC2CCCCN3CC[C@H](C3)N4C(=O)c5ccccc45

Example 335

5

Example 336

Additional compounds falling within the scope of the present invention are described by the following structures. Substituents for each example are identified in the table following each structure.

Table B

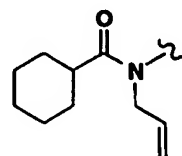
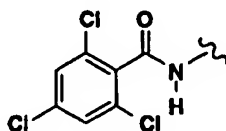
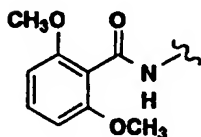
(Where W is H, H or O)

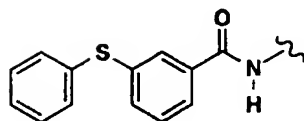
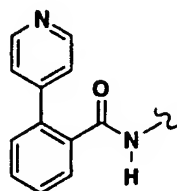
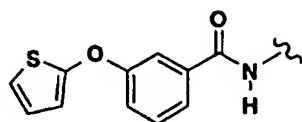
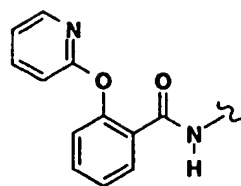
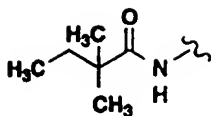
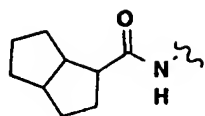
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where R<sup>1x</sup> is (a), (b), (c), (d) or (e) as in Table A

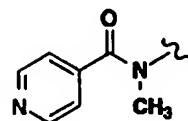
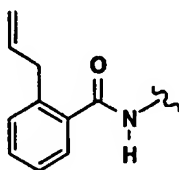
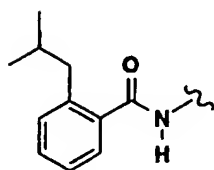
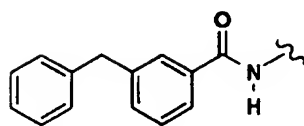
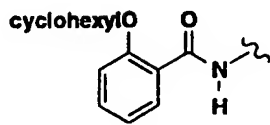
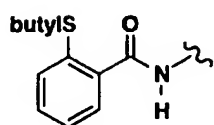
Examples of q<sup>1</sup>

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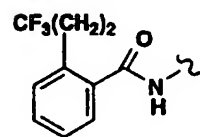
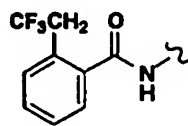
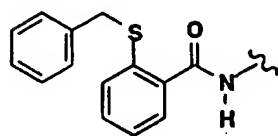
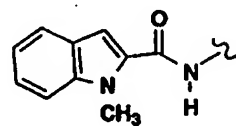
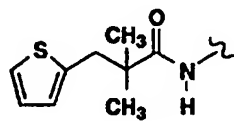
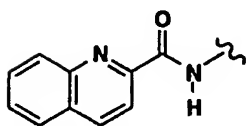


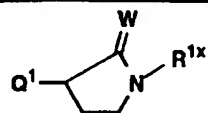


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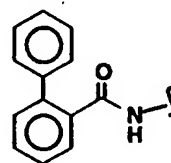
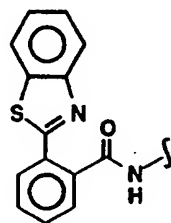
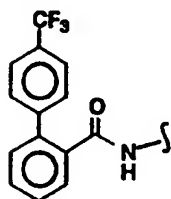
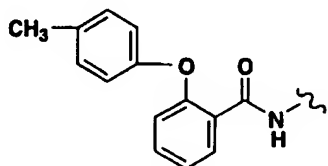
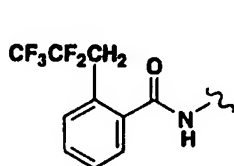
**Table B (continued)**

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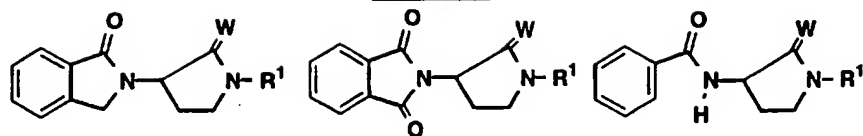
**Examples of Q<sup>1</sup>**

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5

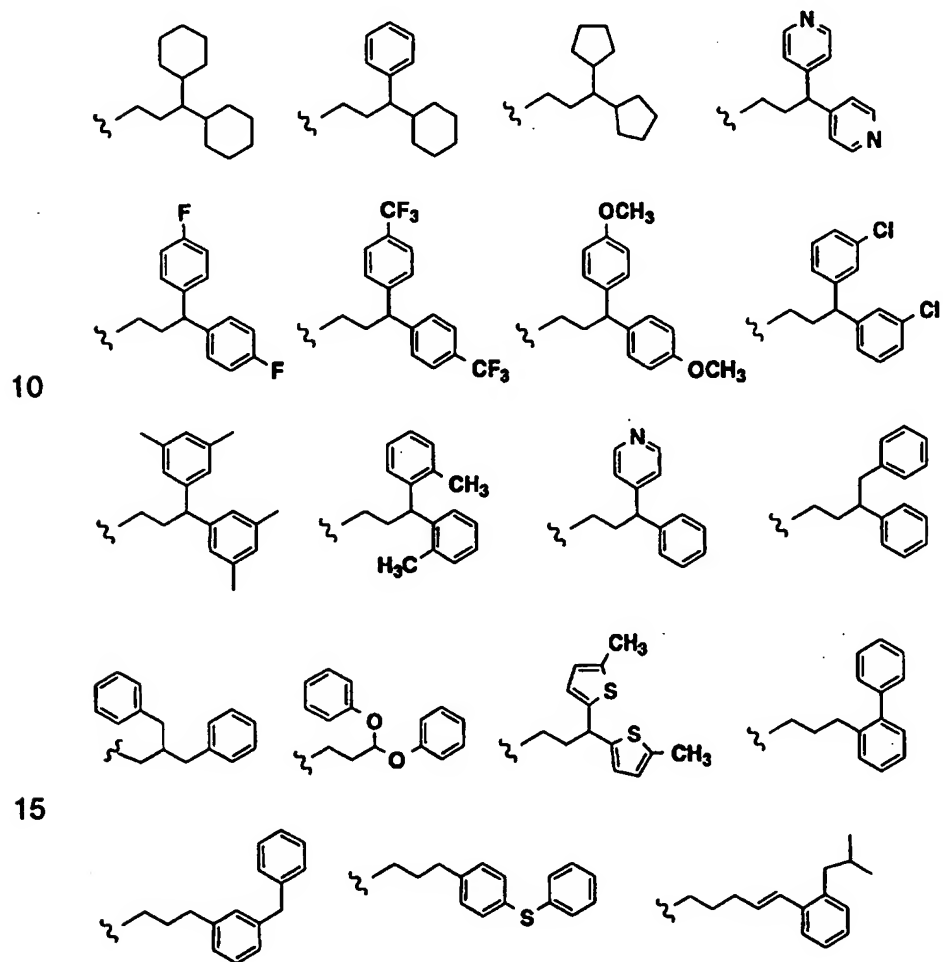


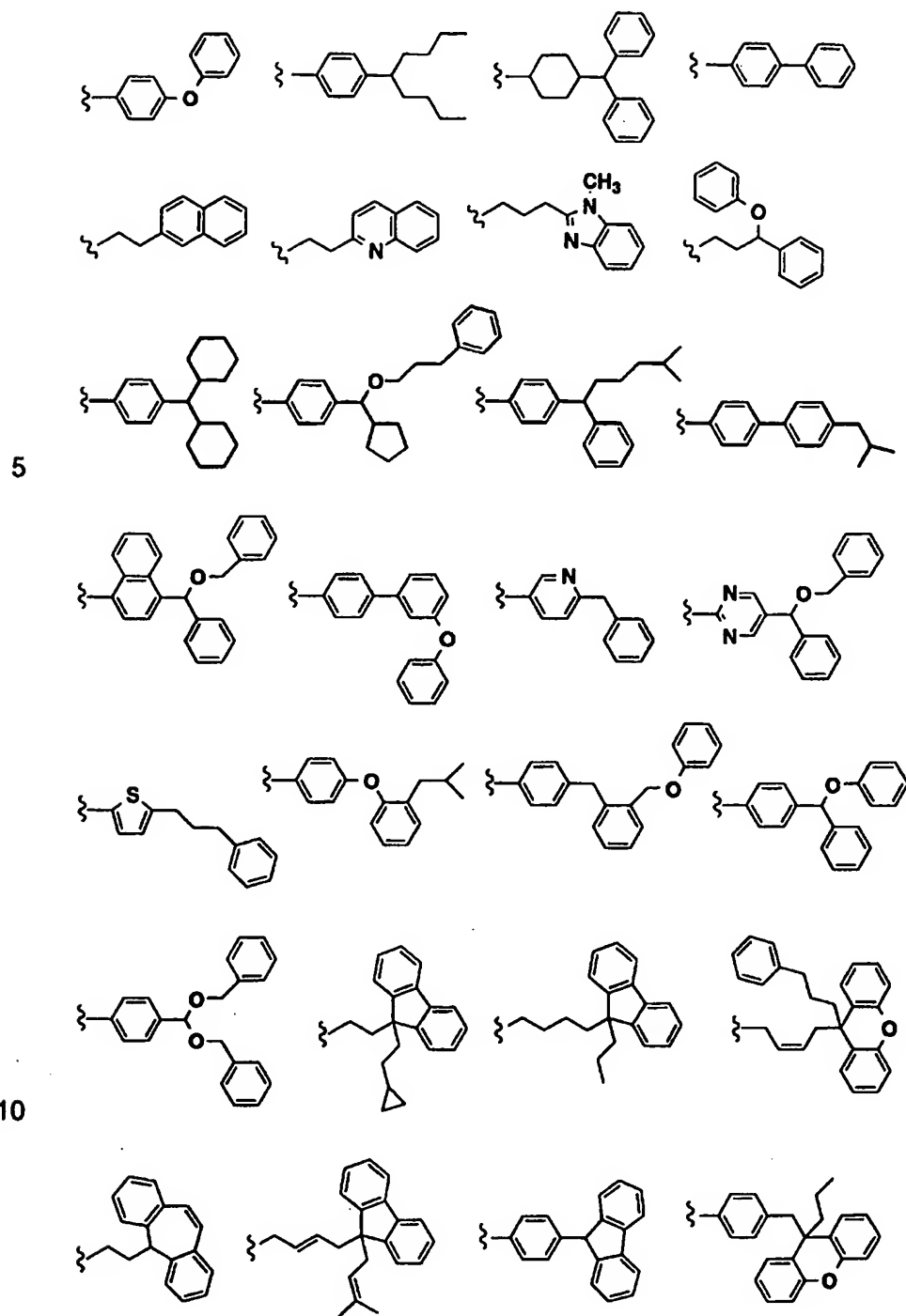
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**Table C**

(Where W is H, H or O)

5

**Examples of R<sup>1</sup>**

**Table C (continued)**

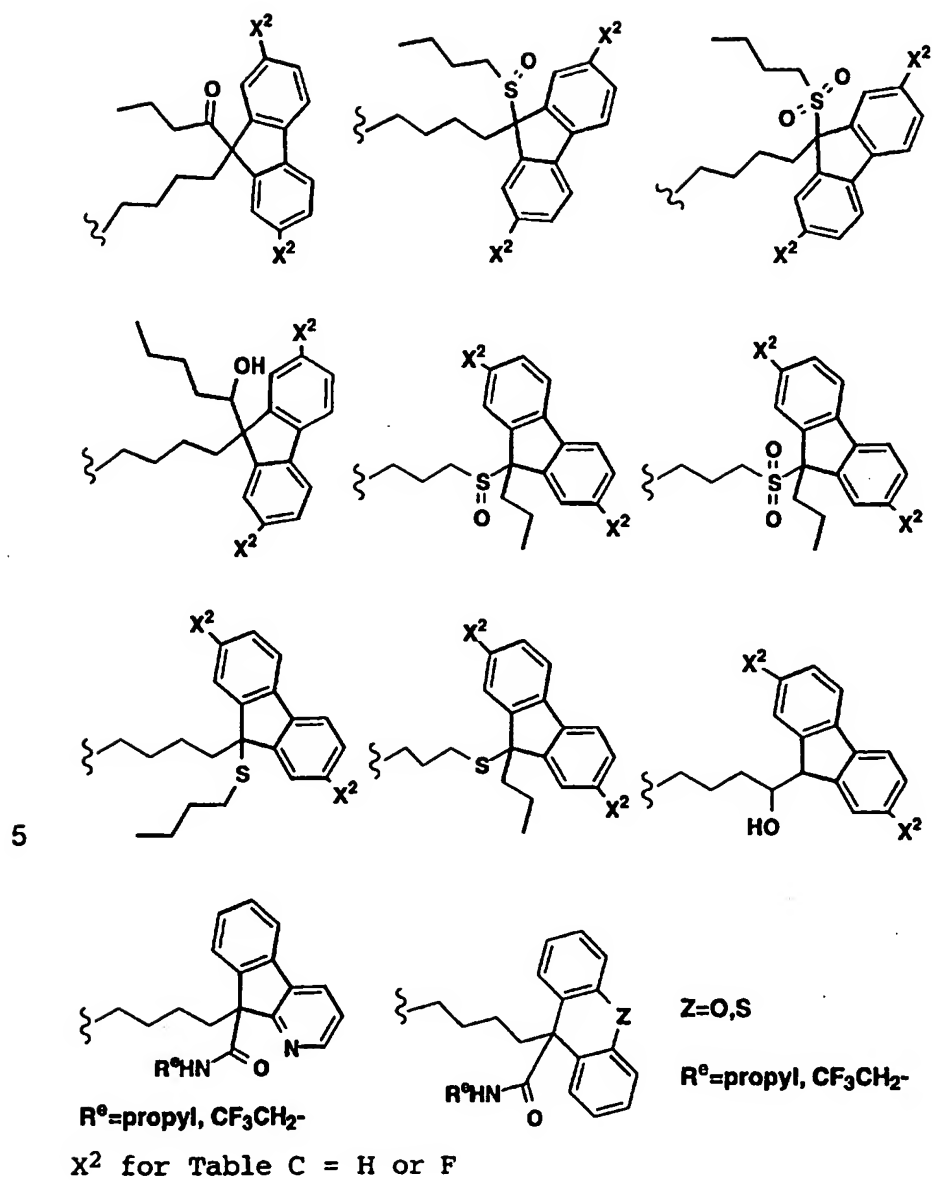
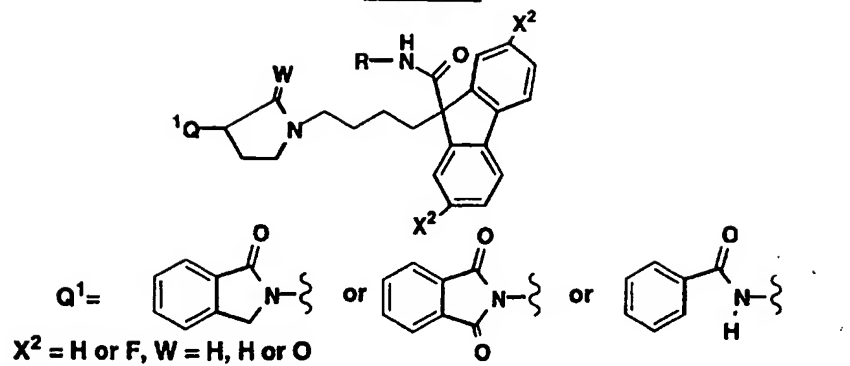
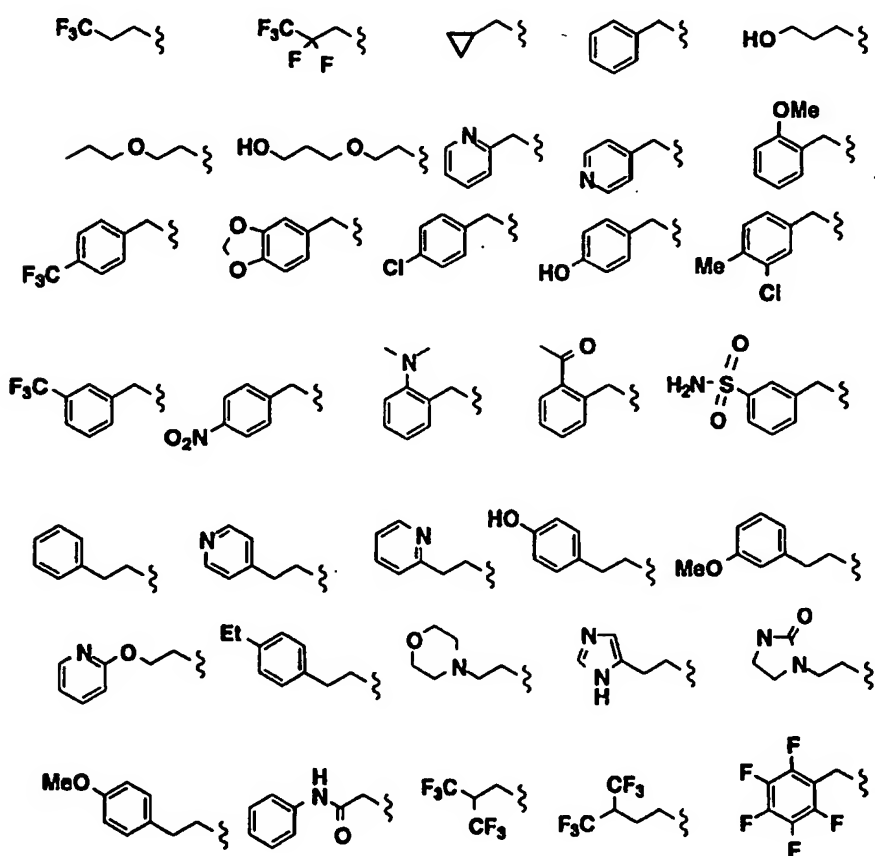


Table D

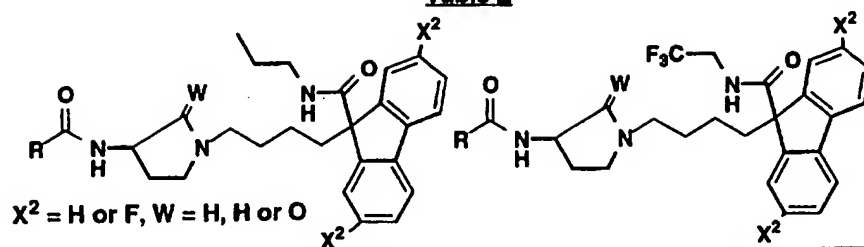


Example of R





### **Table E**



### Example of R

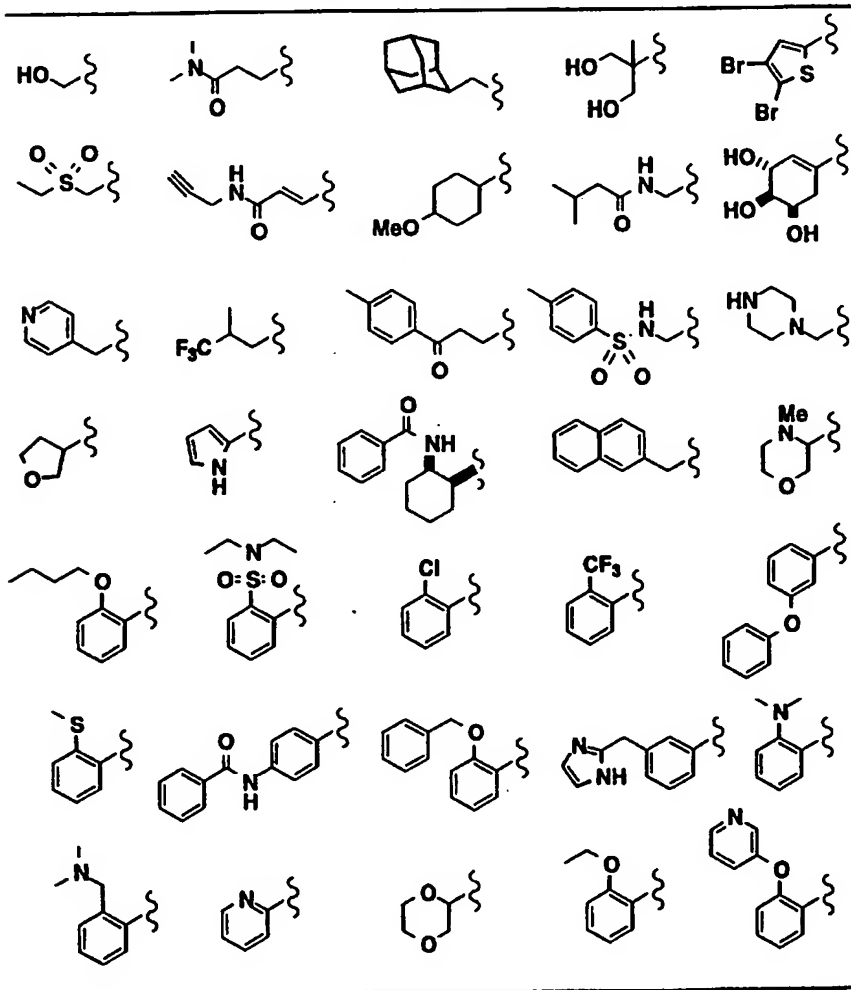


Table E (Cont'd)

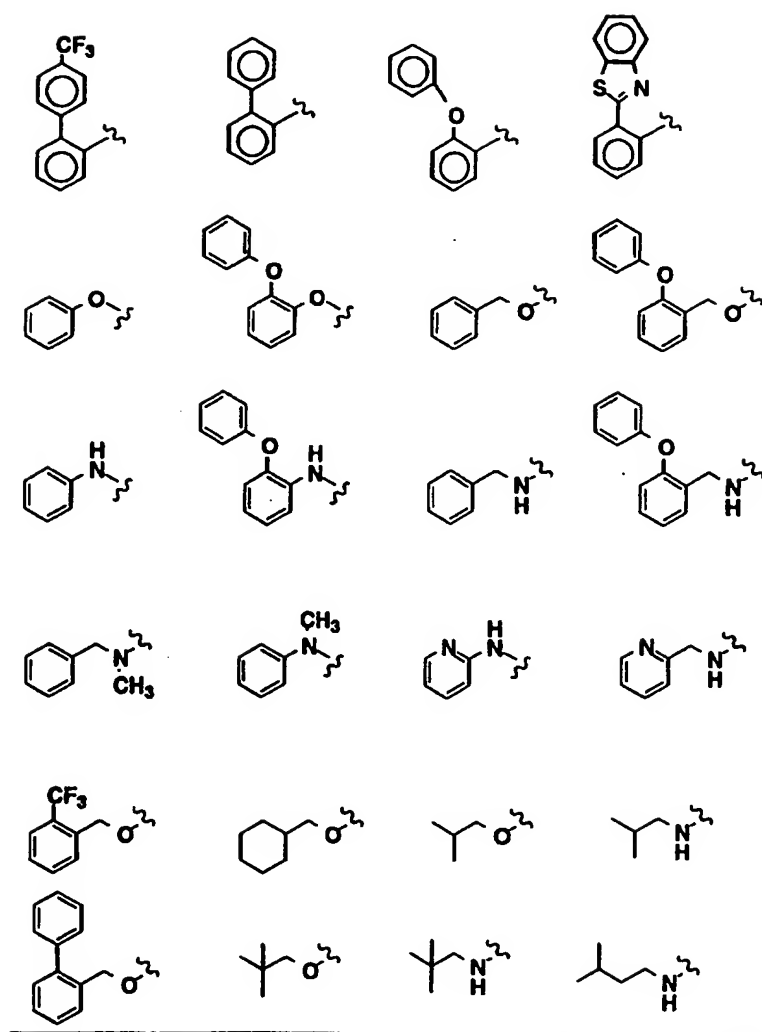
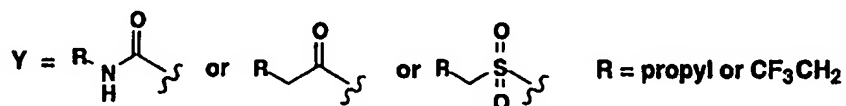
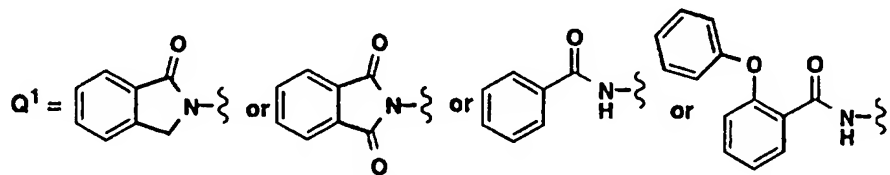
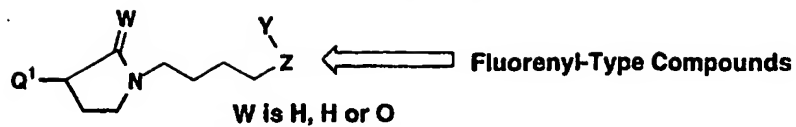


Table F



Fluorenyl-Type Rings: Z =

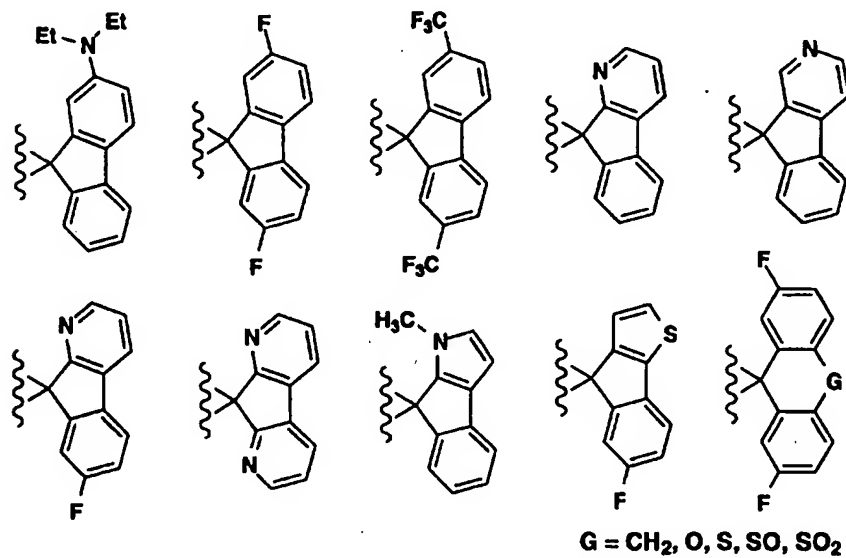
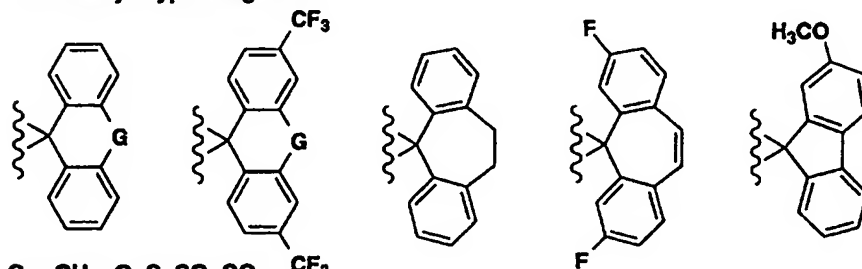
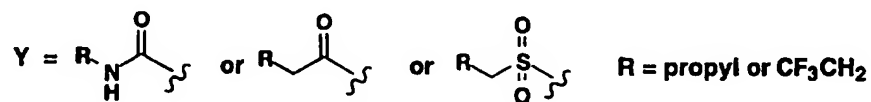
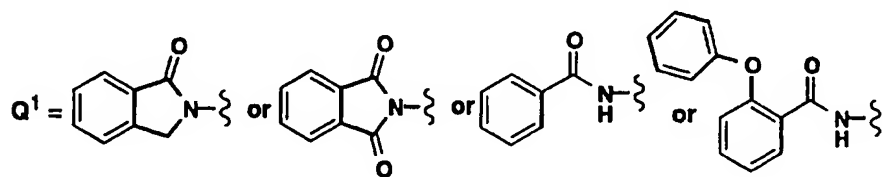
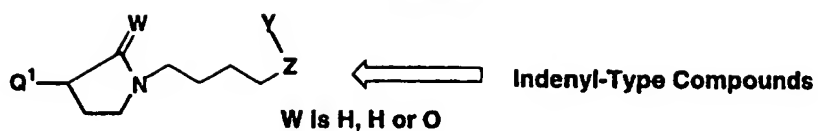


Table G



Indenyl-Type Rings: Z =

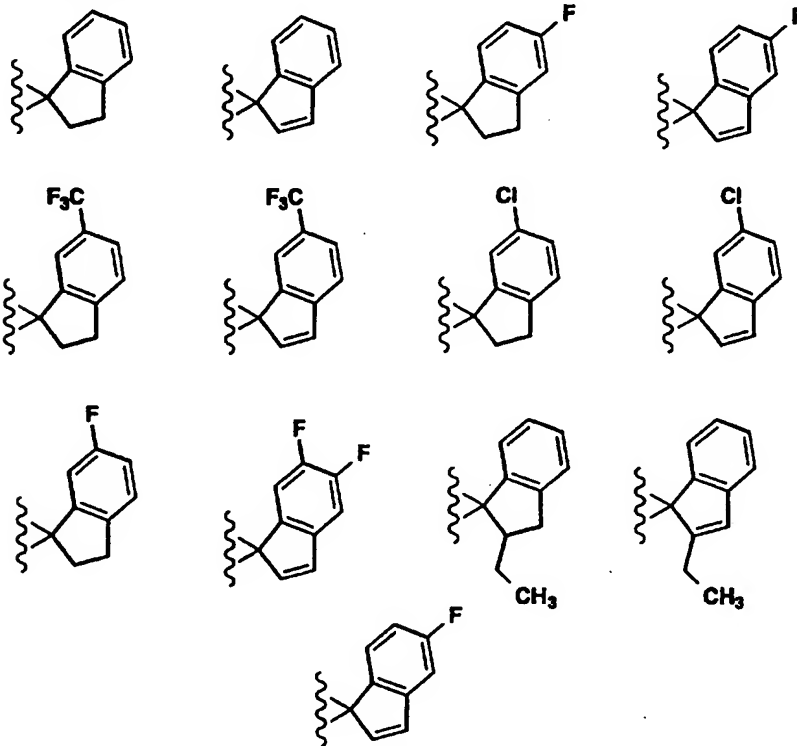


Table G (cont'd)

Indenyl-Type Rings: Z =

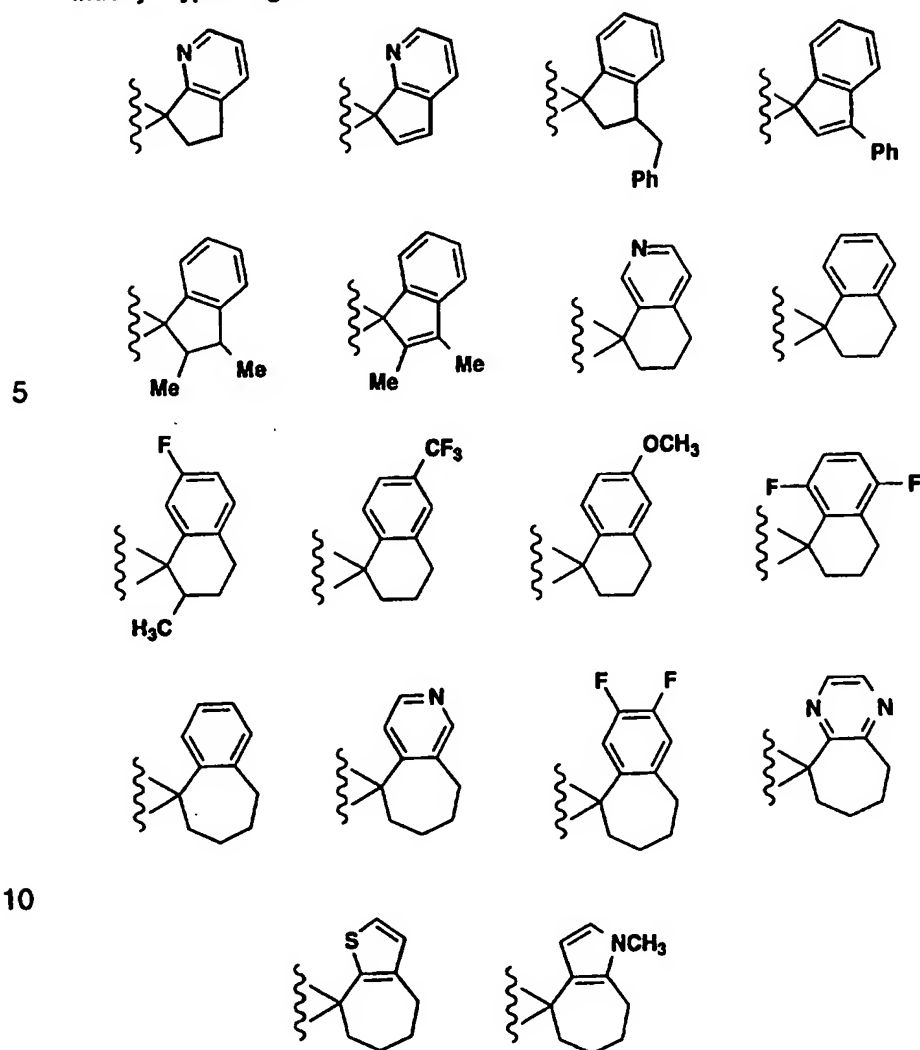
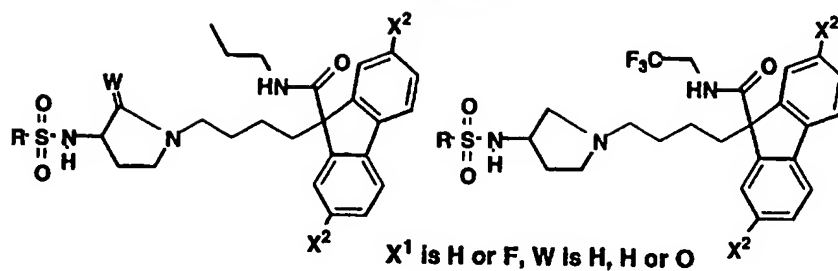
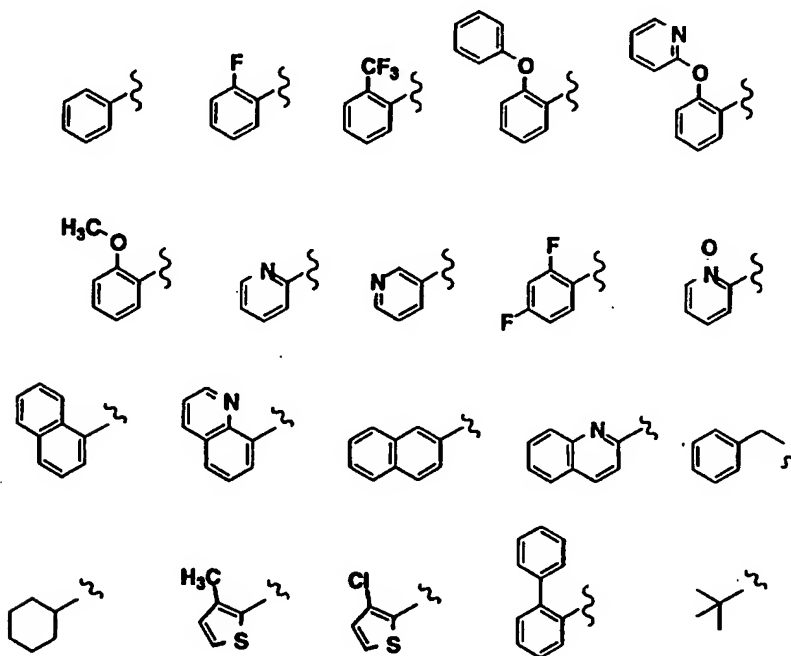


Table H



## Example of R



Example 337

5 cis-9-[4-[3-(2,3-Dihydro-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, N-oxide

Example 338

10 2-[1-[4-[9-(Butylsulfonyl)-9H-fluoren-9-yl]butyl]-3-pyrrolidinyl]-2,3-dihydro-1H-isoindol-1-one

Example 339

15 9-[4-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-1-pyrrolidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

Example 340

20 9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

Example 341

25 9-[4-[[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

Example 342

30 9-[4-[[3-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

Example 343

35 2,7-Difluoro-9-[4-[[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

**Example 344**

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

5

**Example 345**

2,3-Dihydro-2-[1-[4-[9-(1-oxopentyl)-9H-fluoren-9-yl]butyl]-3-pyrrolidinyl]-1H-isoindol-1-one, monohydrochloride

10

**Example 346**

2,3-Dihydro-2-[1-(1-oxo-3,3-diphenylpropyl)-3-pyrrolidinyl]-1H-isoindol-1-one

15

**Example 347**

[1-[4-[9-[(Propylamino)carbonyl]-9H-fluoren-9-yl]-butyl]-3-pyrrolidinyl]carbamic acid, phenylmethyl ester, monohydrochloride

20

**Example 348**

9-[4-[3-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride salt

25

**Example 349**

9-[4-[3-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride salt

30

**Example 350**

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide

**Example 351**

35

9-[4-[3-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-pyrrolidinyl]-butyl]-N-propyl-9H-fluorene-9-carboxamide



Example 352

9-[4-[3-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,3,3,4,4,4-heptafluorobutyl)-9H-fluorene-9-carboxamide, monohydrochloride

5

Example 353

9-[4-[[3-[(1,1-Dimethylethoxy) carbonyl] amino]-1-pyrrolidinyl]butyl]-3,6-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

10

Example 354

1-[4-[3-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-2-methyl-N-(2,2,2-trifluoroethyl)-1H-indene-1-carboxamide

Example 355

15

9-[4-[3-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,3,3,3-pentafluoropropyl)-9H-fluorene-9-carboxamide, monohydrochloride

Example 356

20

1-[4-[3-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-1H-indene-1-carboxamide

Example 357

25

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-3,6-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

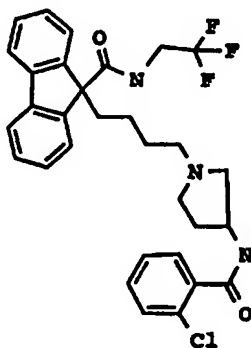
Example 358

3,6-Difluoro-9-[4-[3-[(2-phenoxybenzoyl) amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

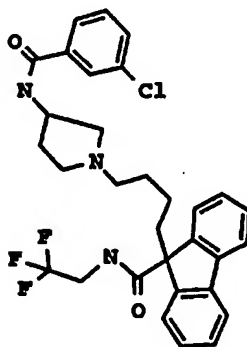
Please note that in the Examples 359 to 477 for structures bearing only two single bonded substituents to nitrogen, the third substituent is always hydrogen, but it is not shown explicitly in the structures. Also, please note that in the Examples 359 to 475 for structures bearing oxygen and sulfurs with only one single bonded substituent, the second substituent is always hydrogen, but is not shown explicitly in the structures.

Example No.

359

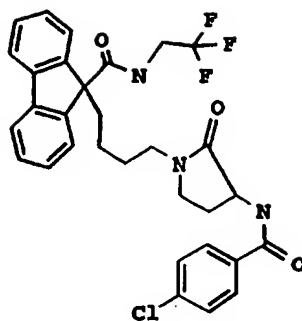


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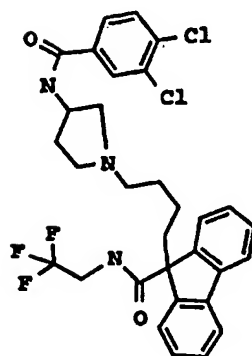


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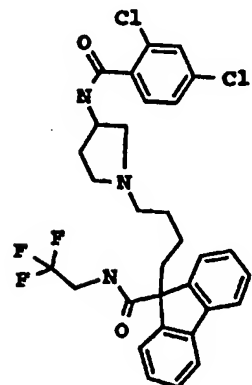
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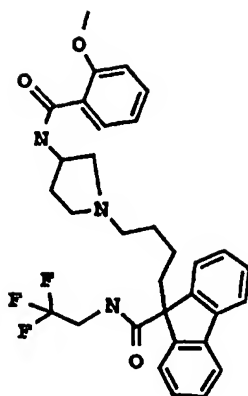
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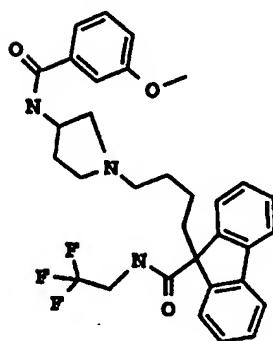
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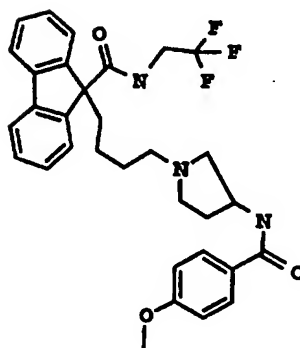
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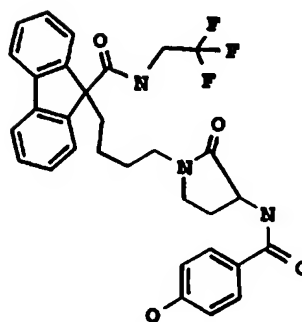
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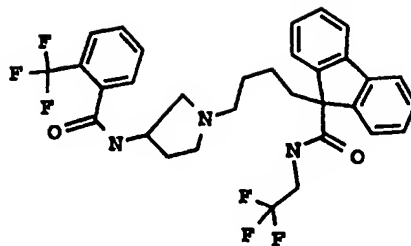
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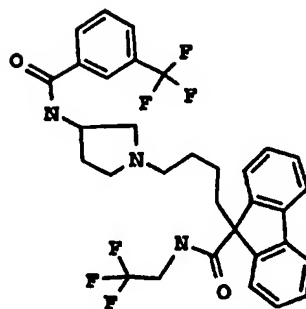
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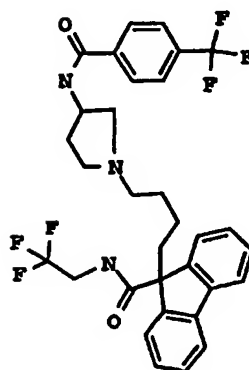
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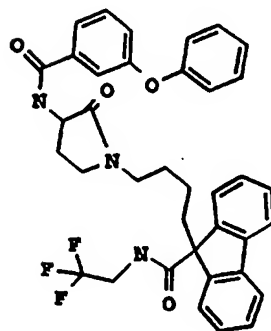
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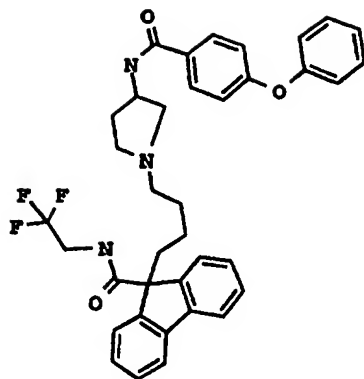
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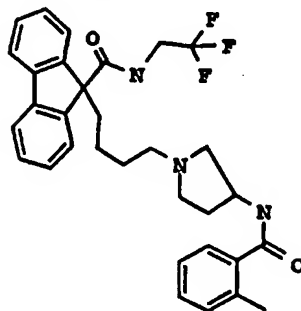
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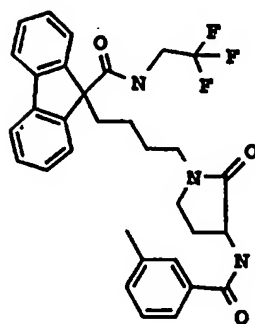
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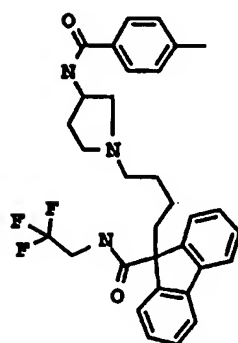
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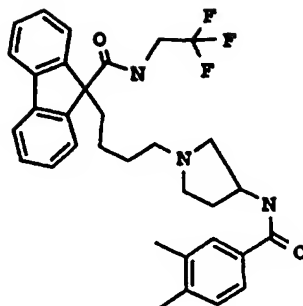
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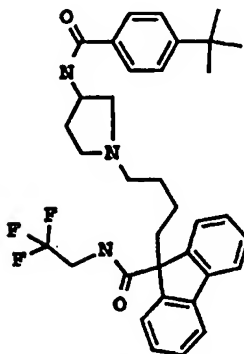
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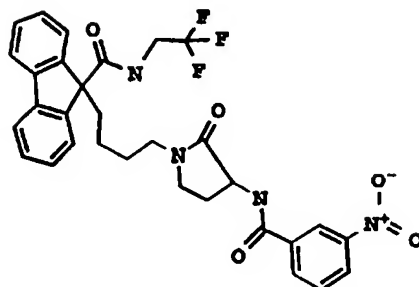
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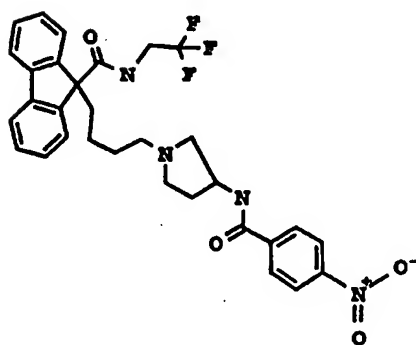
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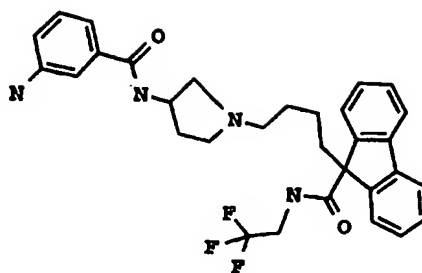
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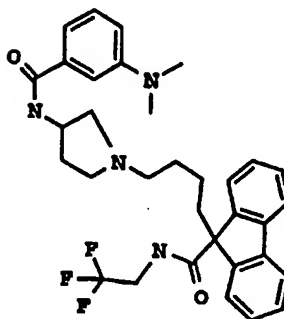
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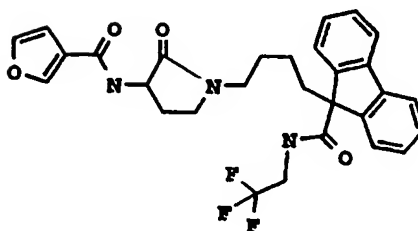
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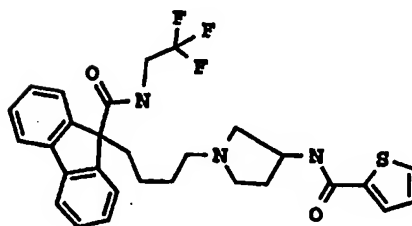
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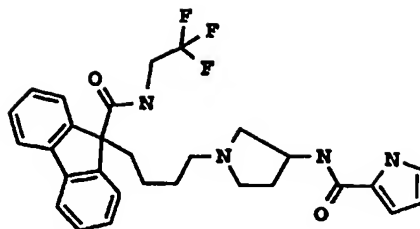


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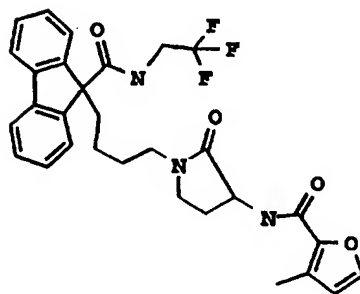




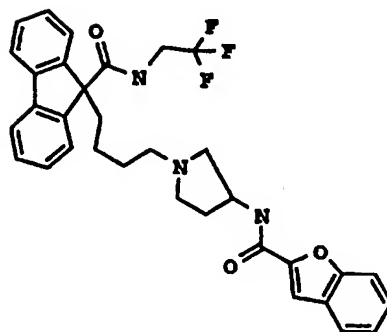
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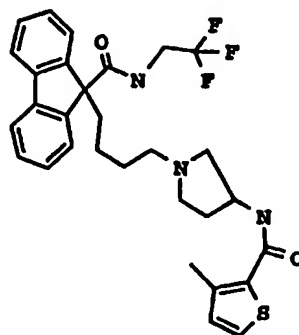
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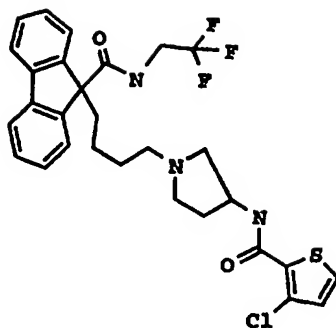
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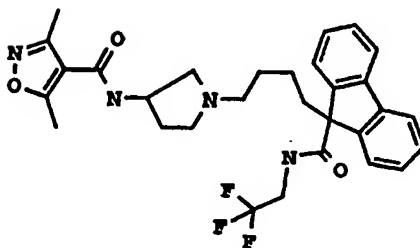
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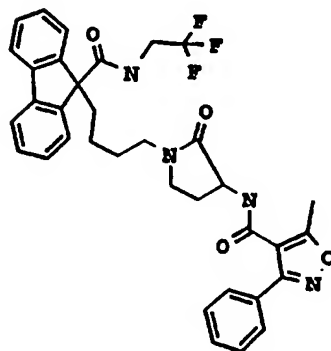
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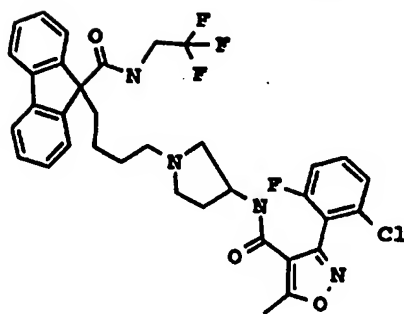
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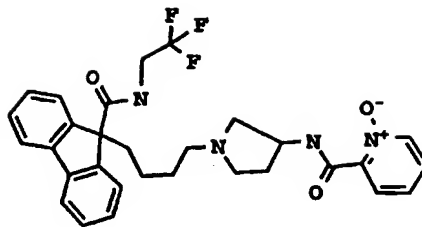
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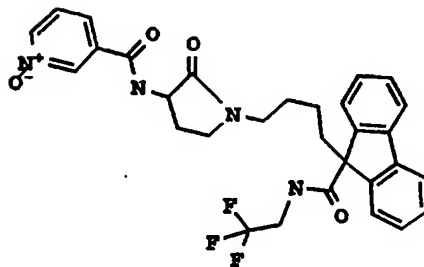
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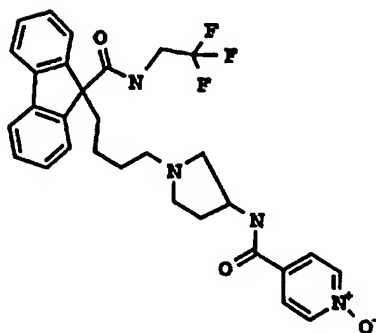
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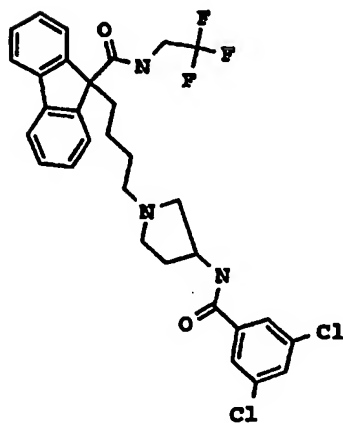
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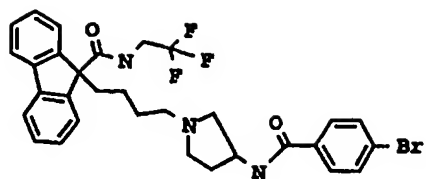
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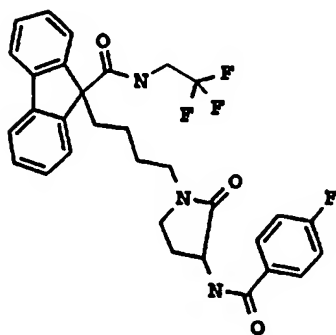
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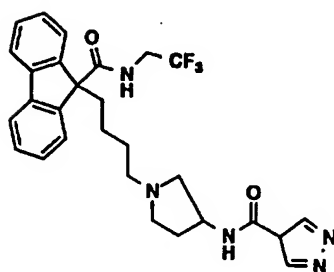
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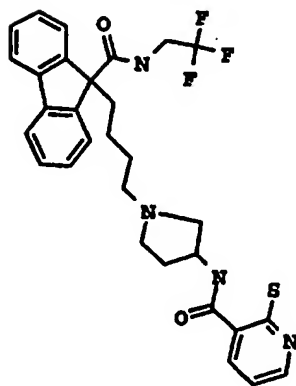
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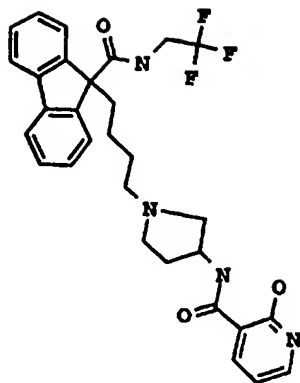
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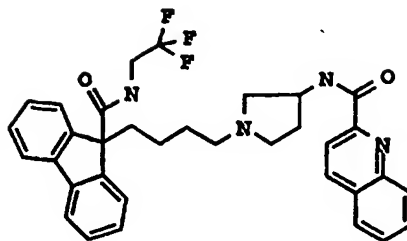
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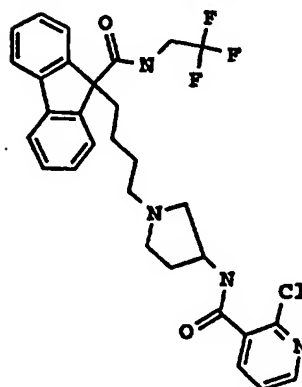
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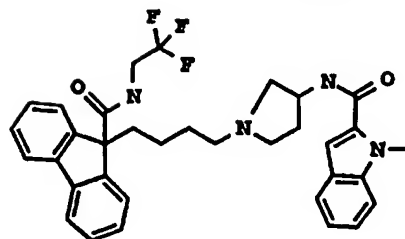
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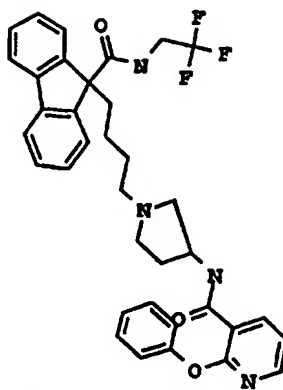
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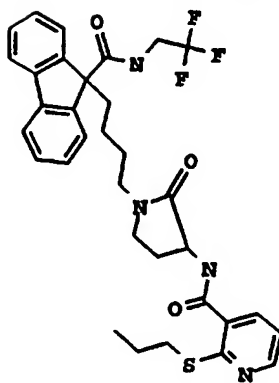
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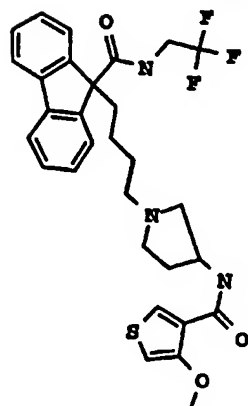
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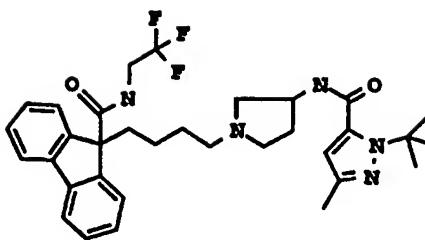
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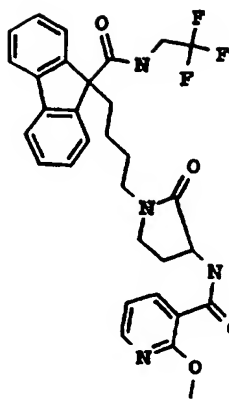
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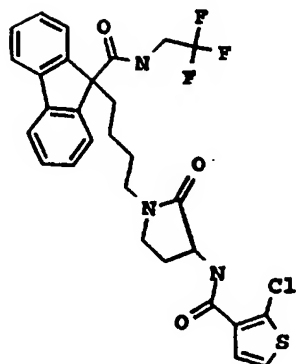
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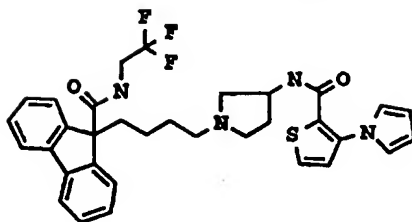
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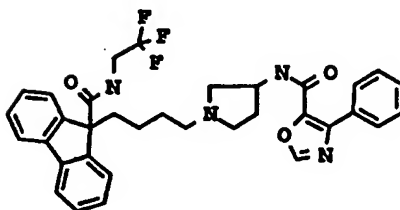
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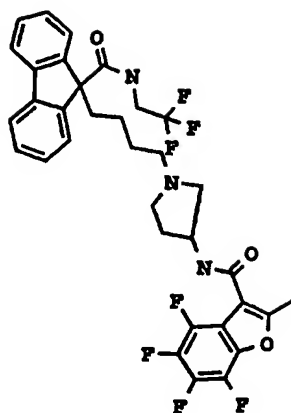
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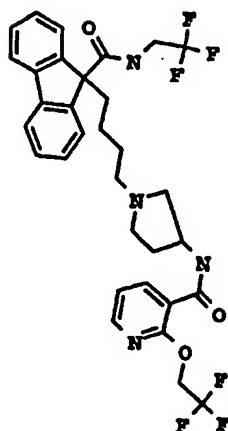
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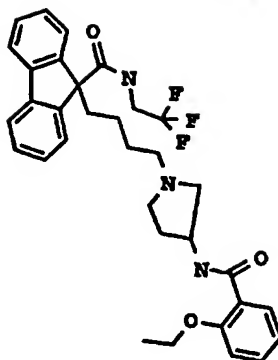
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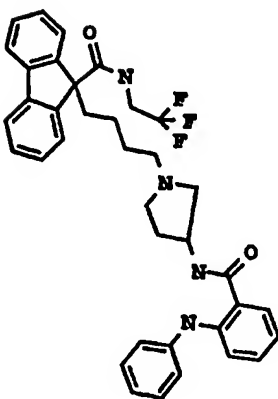
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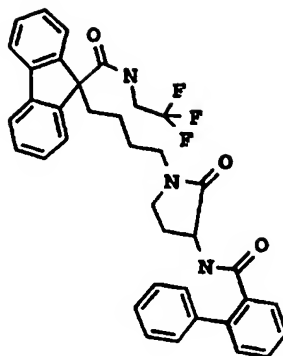


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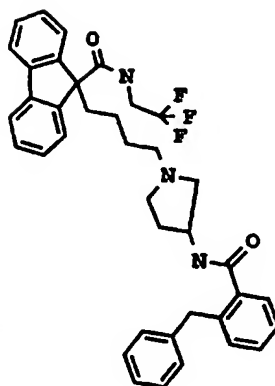




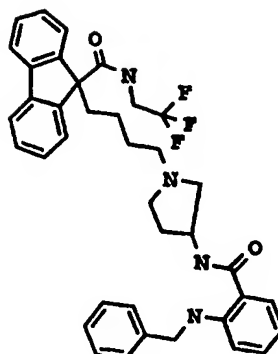
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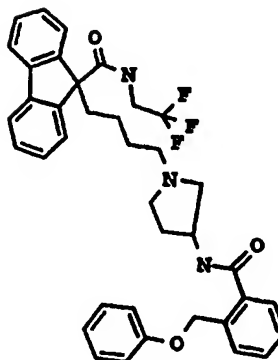
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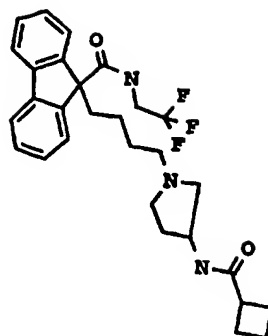
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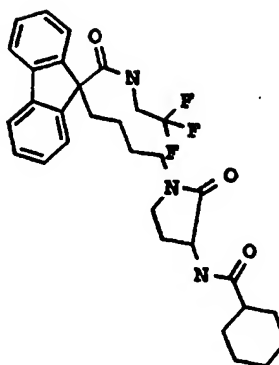
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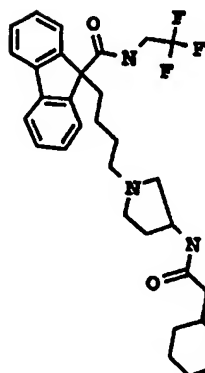
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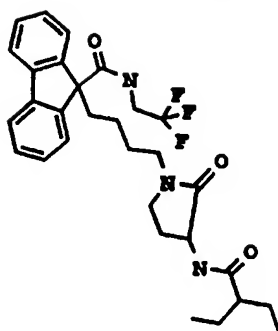
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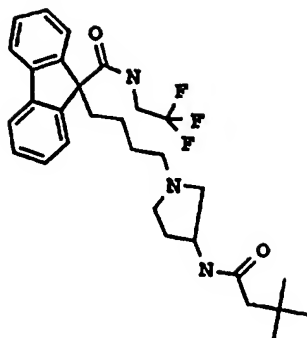
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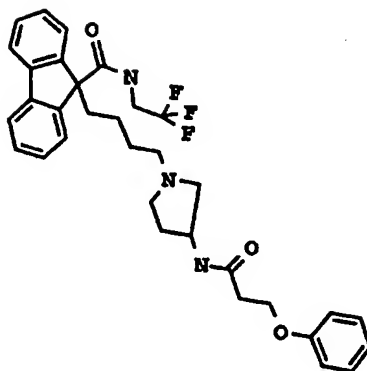
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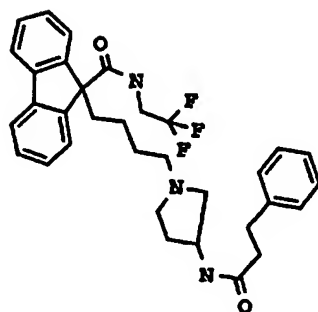
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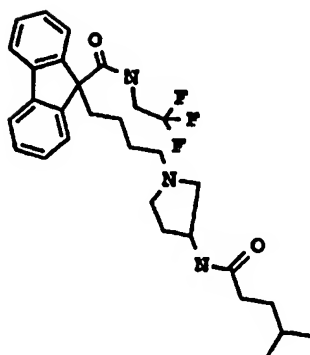
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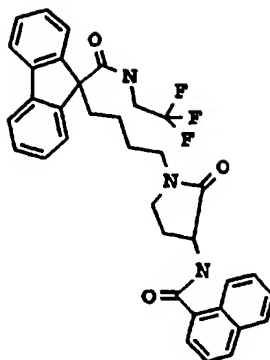
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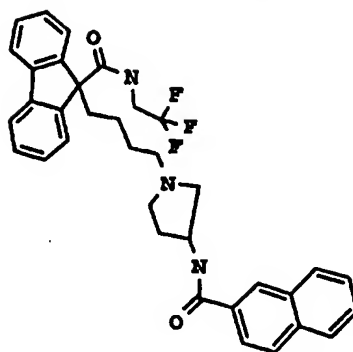
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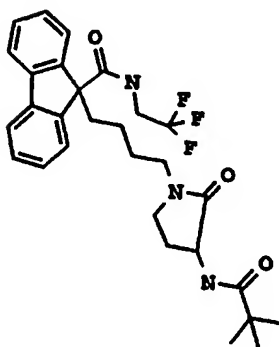
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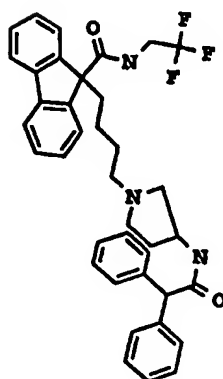
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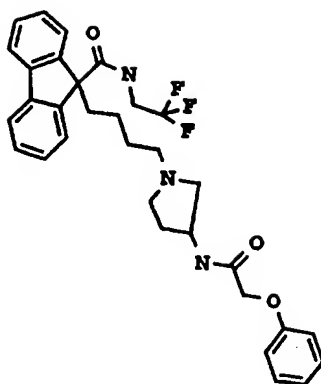
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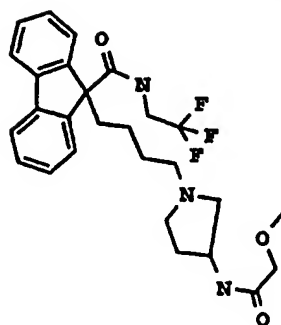
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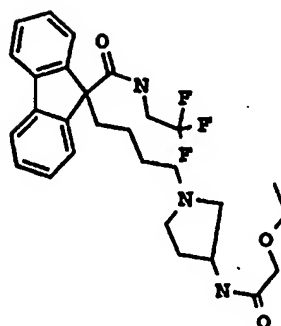
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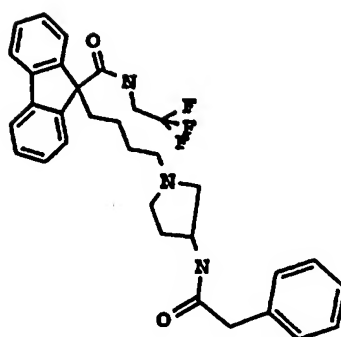
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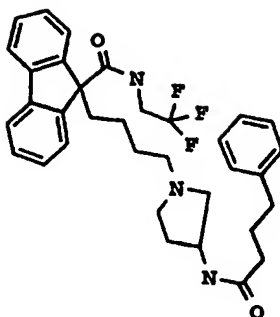
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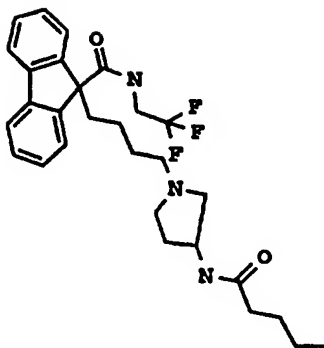
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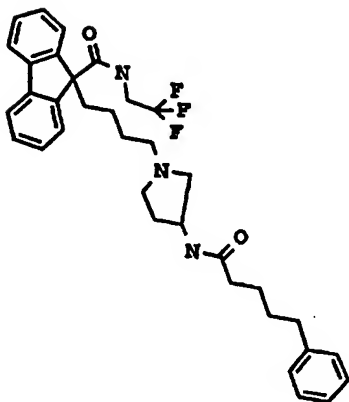
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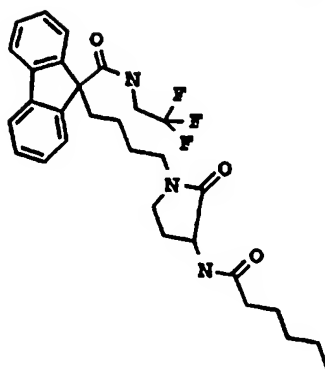
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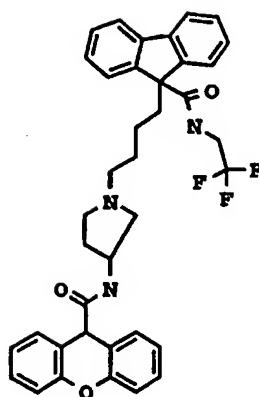
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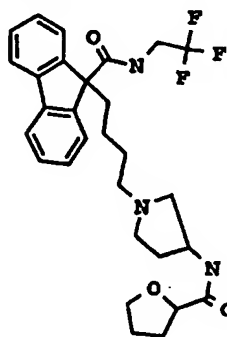
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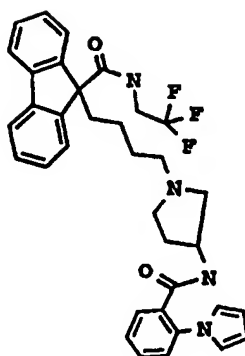
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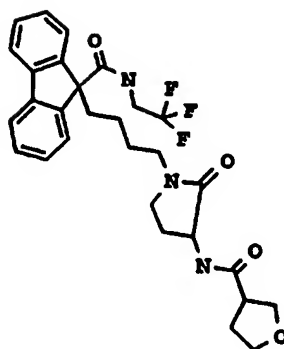
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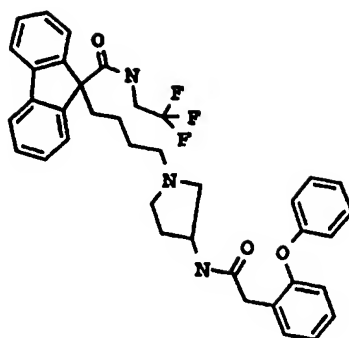
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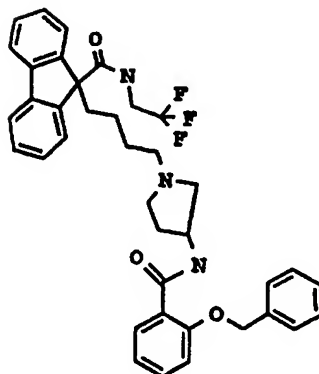
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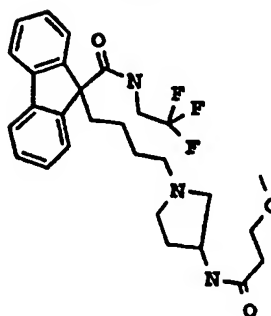
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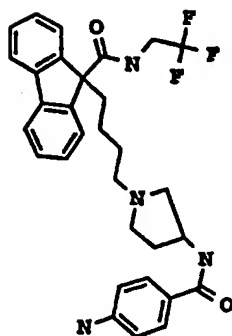
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446

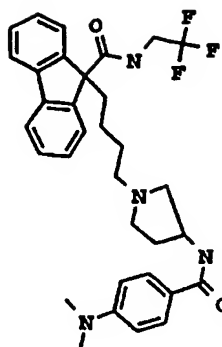


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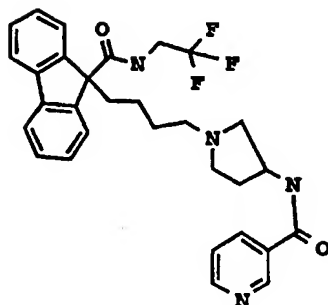




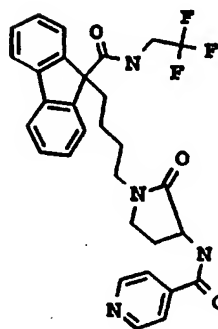
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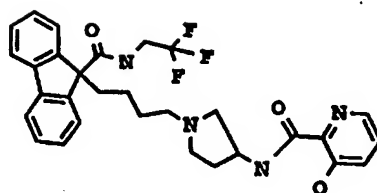
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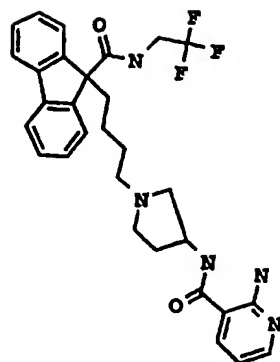
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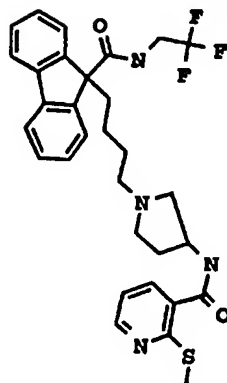
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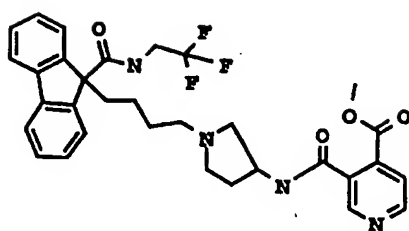
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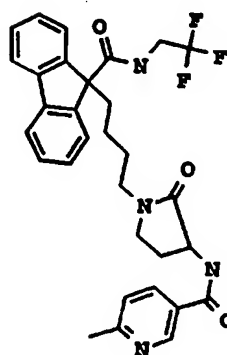
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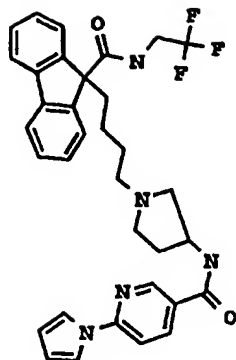
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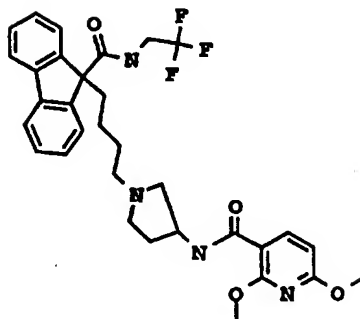
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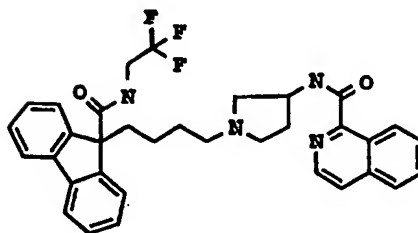
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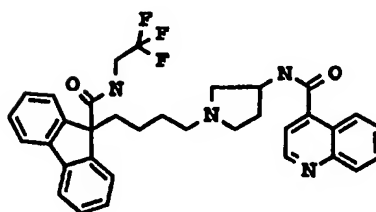
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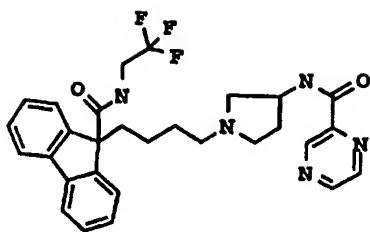
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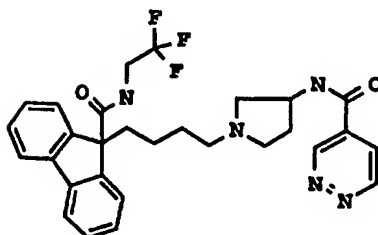
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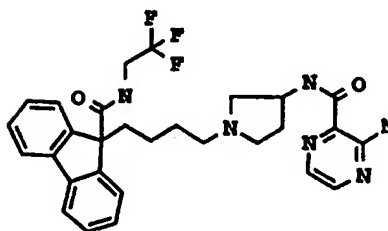
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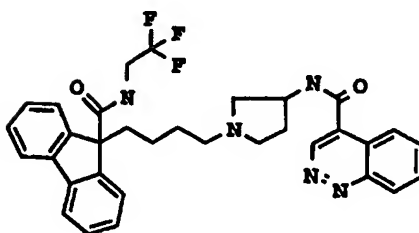
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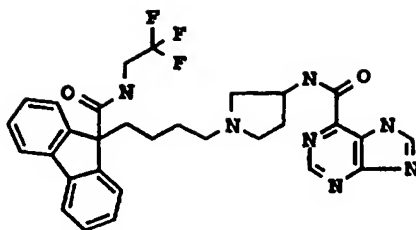
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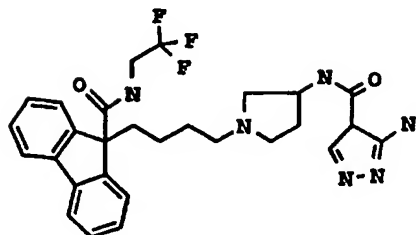
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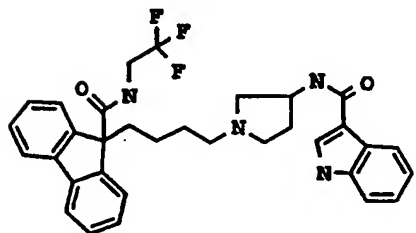
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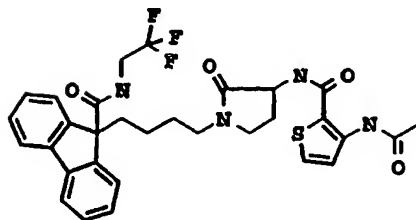
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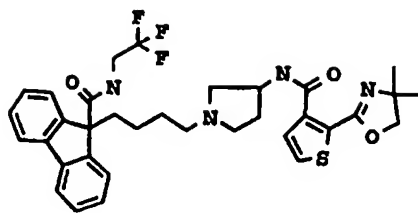
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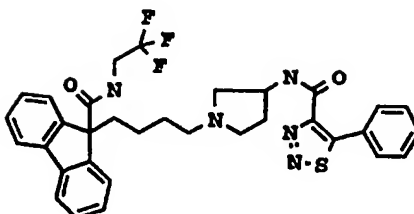
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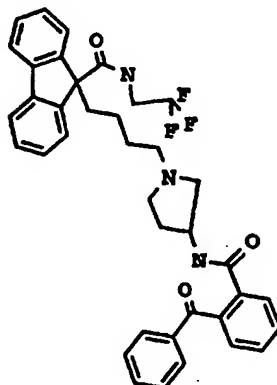
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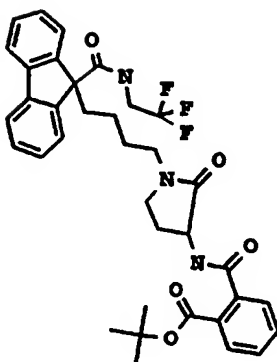
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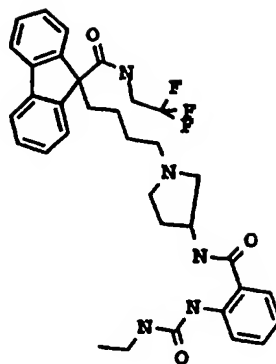
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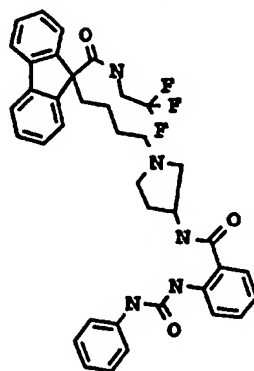
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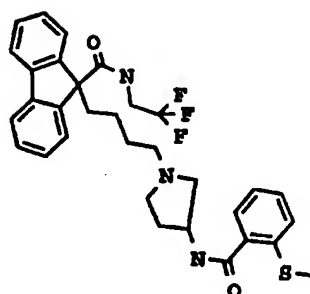
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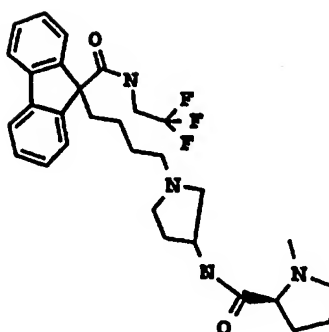
473



474



475

**Example 476**

9-[4-[3-[(Phenoxycarbonyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

5

Example 477

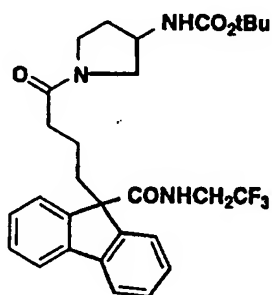
9-[4-[3-[(Phenylamino)carbonyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

10

Example 478

9-[4-[3-[(Phenylsulfonyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

15

Example 479Example 480

20

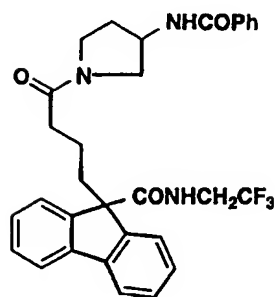
cis-9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N-oxide

Example 481

25

9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-4-oxobutyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



Example 482

5

Example 483

9-[4-[3-[[ (1,1-Dimethylethoxy) carbonyl] amino]-1-pyrrolidinyl]pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

10

Example 484

9-[4-[3-[[ (2-Phenoxyphenyl) sulfonyl] amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

15

Example 485

[1-[[[2-[9-[[ (2,2,2-Trifluoroethyl) amino] carbonyl]-9H-fluoren-9-yl]ethyl]amino]carbonyl]-3-pyrrolidin-yl]carbamic acid, 1,1-dimethylethyl ester

20

Example 486

9-[2-[[[3-(Benzoylamino)-1-pyrrolidinyl] carbonyl]-amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

25

Example 487

3-[[ (1,1-Dimethylethoxy) carbonyl] amino]-1-pyrrolidinecarboxylic acid, 2-[9-[[ (2,2,2-trifluoroethyl) amino] carbonyl]-9H-fluoren-9-yl], ethyl ester

30

Example 488

3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidine-  
carboxylic acid, 2-[9-[(2,2,2-trifluoroethyl)-  
amino]carbonyl]-9H-fluoren-9-yl]ethyl ester

5

Example 489

9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-  
pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-  
carboxamide, monohydrochloride

10

Example 490

9-[2-[[[3-[(2-Phenoxybenzoyl)amino]-1-  
pyrrolidinyl]carbonyl]amino]ethyl]-N-(2,2,2-  
trifluoroethyl)-9H-fluorene-9-carboxamide

15

Example 491

3-(Benzoylamino)-1-pyrrolidinecarboxylic acid,  
2-[9-[(2,2,2-trifluoroethyl)amino]carbonyl]-  
9H-fluoren-9-yl]ethyl ester

20

Example 492

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]pentyl]-  
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-  
carboxamide, monohydrochloride

25

Example 493

9-[4-[3-[(1,1-Dimethylethoxy)carbonyl]amino]-  
1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-  
9H-thioxanthene-9-carboxamide

30

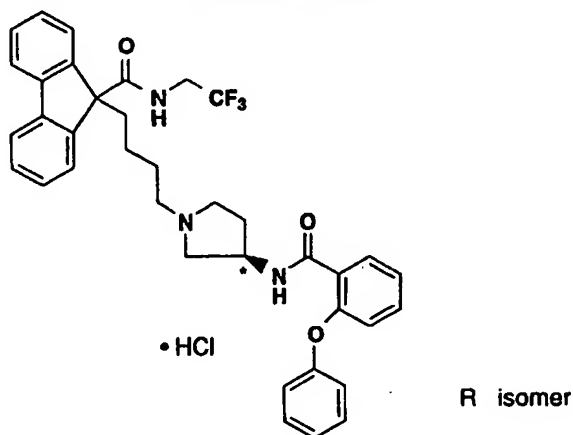
Example 494

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]-  
butyl]-N-(2,2,2-trifluoroethyl)-9H-  
thioxanthene-9-carboxamide

Example 495

9-[4-[3-[[[(2-Phenoxyphenyl)carbonyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide

5

Example 496

(R)-9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

m.p. 112-115°C

10 MS (ES, + ions): m/z 628 (M+H)

Anal. Calcd for C<sub>37</sub>H<sub>36</sub>F<sub>3</sub>N<sub>3</sub>O<sub>3</sub> + 1.0 HCl + 0.9 H<sub>2</sub>O:

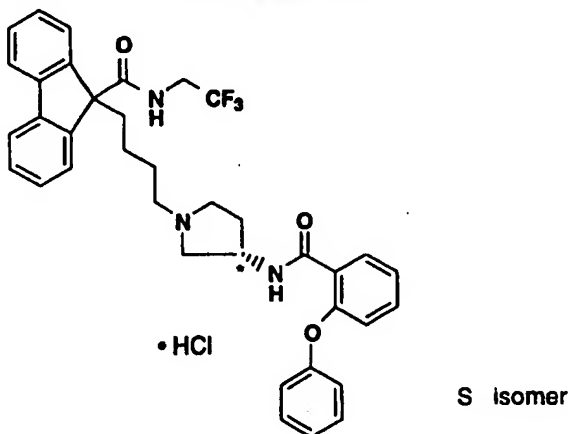
C, 65.32; H, 5.75; N, 6.18; F, 8.38;

Cl, 5.21

Found: C, 65.30; H, 5.59; N, 6.01; F, 8.83;

15

Cl, 5.35.

Example 497

(S)-9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

m.p. 98-103°C

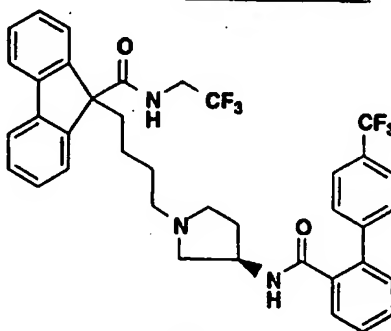
MS (ES, + ions): m/z 628 (M+H).

5 Anal. Calcd for  $C_{37}H_{36}F_3N_3O_3 + 1.0 \text{ HCl} + 1.5 \text{ H}_2\text{O}$ :

C, 64.30; H, 5.83; N, 6.08; F, 8.25

Found: C, 64.34; H, 5.63; N, 5.90; F, 8.46.

#### Example 498



• HCl

10

R isomer  
(R)-N-(2,2,2-Trifluoroethyl)-9-[4-[3-[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

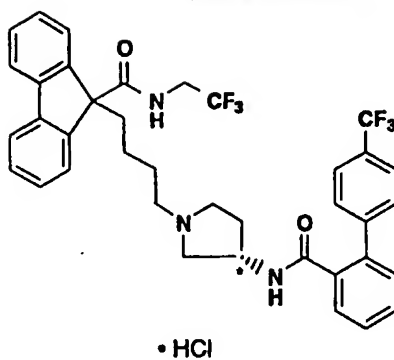
m.p. 108-112°C

MS (ES, + ions): m/z 680 (M+H)

15 Anal. Calcd for  $C_{38}H_{35}F_6N_3O_2 + 1.3 \text{ HCl} + 2.1 \text{ H}_2\text{O}$ :

C, 59.67; H, 5.34; N, 5.49; Cl, 6.03

Found: C, 59.75; H, 5.00; N, 5.18; Cl, 5.75.

Example 499

S isomer

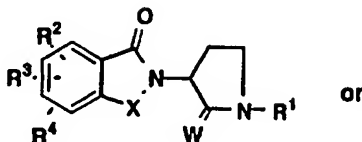
(S)-N-(2,2,2-Trifluoroethyl)-9-[4-[3-[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

5 m.p. 101-105°C

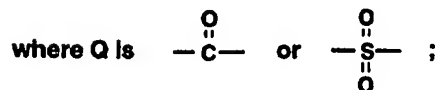
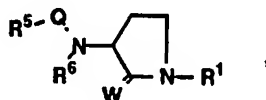
MS (ES, + ions): m/z 680 (M+H).

What Is Claimed Is:

1. A compound which has the structure

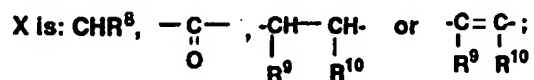


5



W is H, H or O;

10



$\text{R}^8$ ,  $\text{R}^9$  and  $\text{R}^{10}$  are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

15

$\text{R}^1$  is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl, all optionally substituted

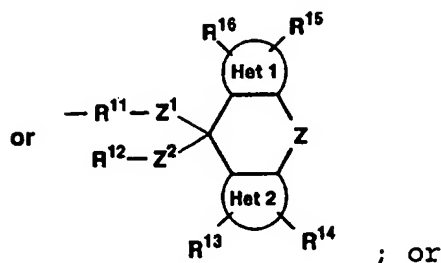
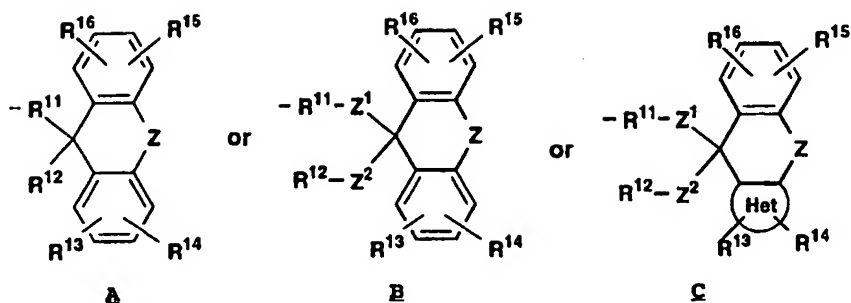
20

through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl,

25

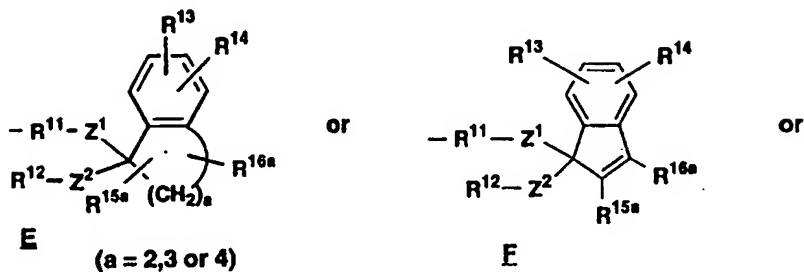
heteroarylalkyl, hydroxy or oxo;

or  $\text{R}^1$  is a fluorenyl-type group of the structure

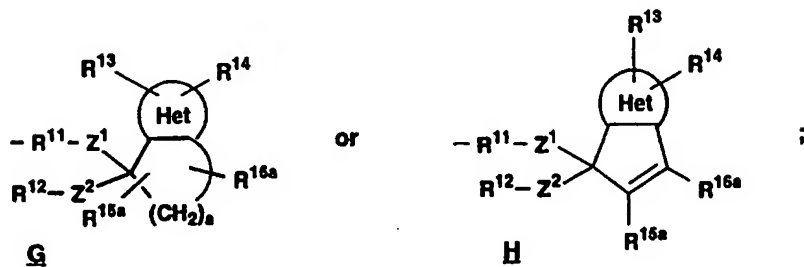


5

$R^1$  is an indenyl-type group of the structure

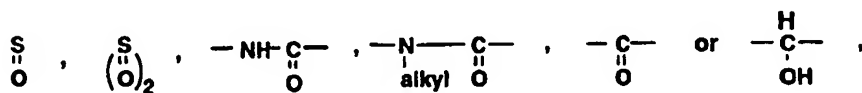


10



15

$Z^1$  and  $Z^2$  are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of  $Z^1$  and  $Z^2$  will be other than a bond;  $R^{11}$  is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene;  $R^{12}$  is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

(1) when  $R^{12}$  is H, aryloxy, alkoxy or arylalkoxy, then  $Z^2$  is  $\begin{array}{c} \text{—NH—C—} \\ \parallel \\ \text{O} \end{array}$ ,  $\begin{array}{c} \text{—N—C—} \\ | \quad \parallel \\ \text{alkyl} \quad \text{O} \end{array}$ ,  $\begin{array}{c} \text{—C—} \\ \parallel \\ \text{O} \end{array}$  or a bond and

(2) when  $Z^2$  is a bond,  $R^{12}$  cannot be heteroaryl or heteroarylalkyl;

$Z$  is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms;  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ , and  $R^{16}$  are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cyclo-heteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

$R^{15a}$  and  $R^{16a}$  are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cyclo-heteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or  $R^1$  is a group of the structure



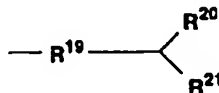
wherein  $p$  is 1 to 8 and  $R^{17}$  and  $R^{18}$  are each independently H, alkyl, alkenyl, aryl, arylalkyl,



heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of R<sup>17</sup> and R<sup>18</sup> being other than H;

or R<sup>1</sup> is a group of the structure

5



wherein R<sup>19</sup> is aryl or heteroaryl;

R<sup>20</sup> is aryl or heteroaryl;

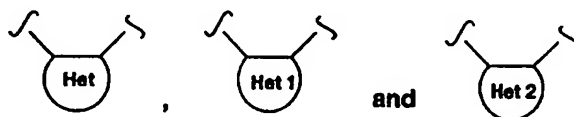
R<sup>21</sup> is H, alkyl, aryl, alkylaryl, arylalkyl,  
 10 aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl,  
 15 arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

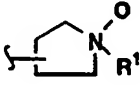
R<sup>5</sup> is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl,  
 20 arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkyl-  
 25 amino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl,  
 30 cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl,  
 35 heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio,

arylthio, heteroarylthio, arylthioalkyl,  
 alkylcarbonyl, arylcarbonyl, arylaminocarbonyl,  
 alkoxy carbonyl, aminocarbonyl, alkynylamino-  
 carbonyl, alkylaminocarbonyl, alkenylamino-  
 5 carbonyl, alkylcarbonyloxy, arylcarbonyloxy,  
 alkylcarbonylamino, arylcarbonylamino, arylsul-  
 finyl, arylsulfinylalkyl, arylsulfonyl, alkylsul-  
 fonyl, arylsulfonylamino, heteroarylcarbonylamino,  
 heteroarylsulfinyl, heteroarylthio, heteroaryl-  
 10 sulfonyl, alkylsulfinyl;

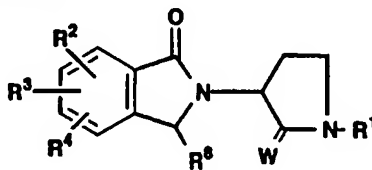
$R^6$  is hydrogen or  $C_1-C_4$  alkyl or  $C_1-C_4$   
 alkenyl; all optionally substituted with 1, 2, 3  
 or 4 groups which may independently be any of the  
 substituents listed in the definition of  $R^5$  set out  
 15 above;



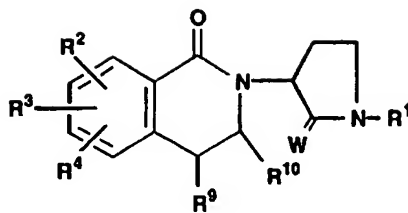
are the same or different and are independently  
 selected from heteroaryl containing 5- or 6-ring  
 20 members; and

an N-oxide  thereof; stereoisomers  
 thereof; and a pharmaceutically acceptable salt  
 thereof.

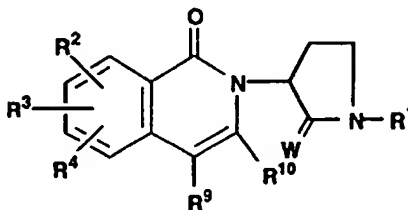
2. The compound as defined in Claim 1  
 25 having the formula



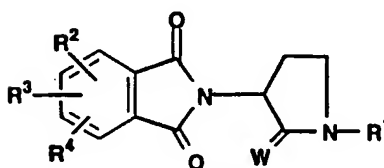
or



or

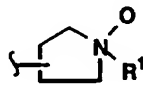


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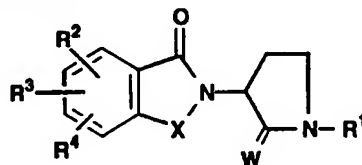
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or



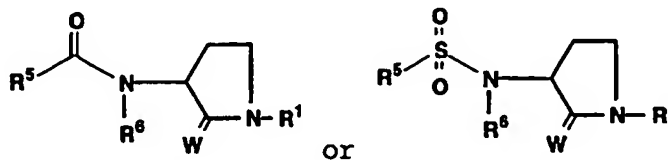
an N-oxide thereof, and a pharmaceutically acceptable salt thereof.

3. The compound as defined in Claim 1  
10 having the formula

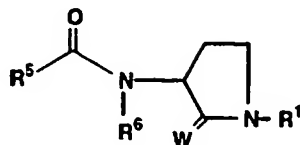


4. The compound as defined in Claim 3  
where R<sup>1</sup> is arylalkyl, heteroalkylalkyl or  
15 cycloalkyl-alkyl.

5. The compound as defined in Claim 1  
having the formula

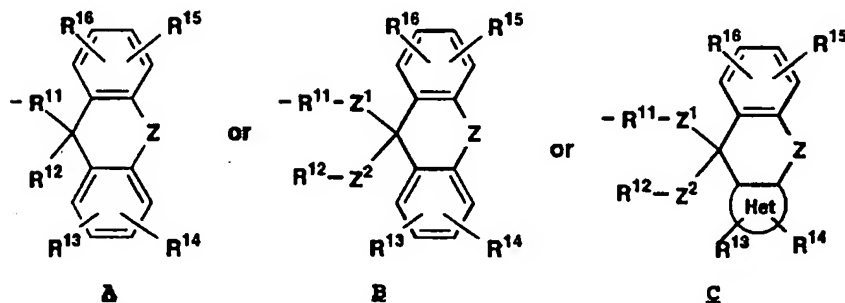


6. The compound as defined in Claim 1  
having the formula

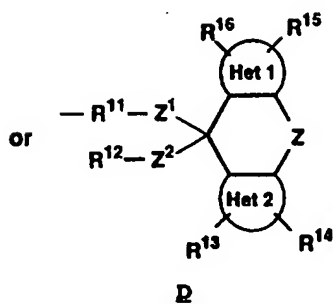


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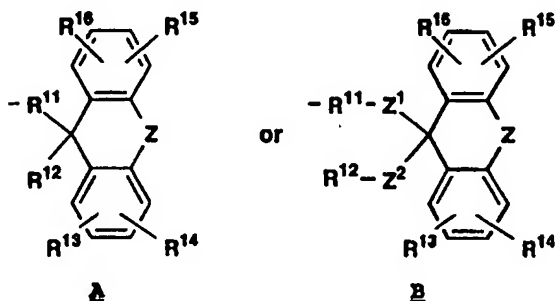
7. The compound as defined in Claim 1  
wherein R<sup>1</sup> is



10



8. The compound as defined in Claim 7  
wherein R<sup>1</sup> is



Z is a bond, O or S;

20 R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> are each H or one of  
R<sup>15</sup> and R<sup>16</sup> and one of R<sup>13</sup> and R<sup>14</sup> are halogen;

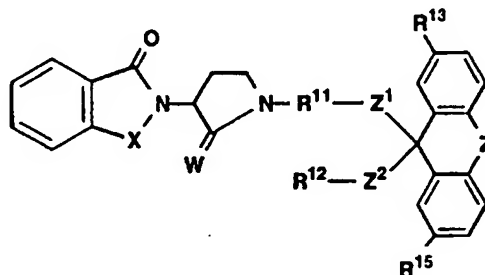
$Z^1$  is a bond or  $C=O$ ;

$R^{11}$  is alkylene or alkenylene;

$R^{12} - Z^2$  is  $R^{12a} - NH - \overset{O}{\parallel} C -$  ; or  $R^{12a} \overset{O}{\parallel} C -$  ;

$R^{12a}$  is alkyl, fluorinated lower alkyl or  
5 polyfluorinated lower alkyl.

9. The compound as defined in Claim 1  
having the structure



10  $Z$  is O, S or a bond;

$R^{13}$  and  $R^{15}$  are independently H or F;

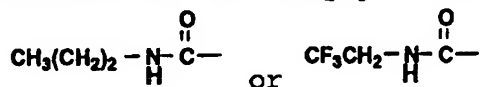
$Z^1$  is a bond;

$R^{11}$  is alkylene;

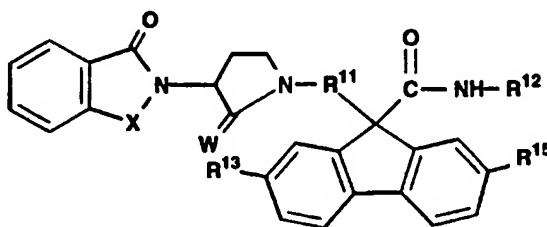
$R^{12} - Z^2$  is  $alkyl - NH - \overset{O}{\parallel} C -$  or  $R^{12a} - NH - \overset{O}{\parallel} C -$  ; and

15  $R^{12a}$  is alkyl, fluorinated lower alkyl or  
polyfluorinated lower alkyl.

10. The compound as defined in Claim 9  
wherein  $R^{11}$  is  $-(CH_2)_4-$ ,  $Z^1$  is a bond, and  $R^{12} - Z^2$  is

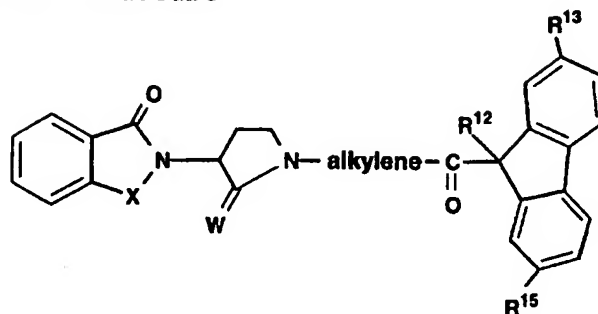


20 11. The compound as defined in Claim 9  
having the structure



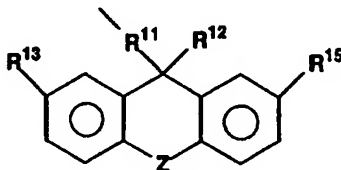
where  $R^{13}$  and  $R^{15}$  are independently H or F, and  $R^{12}$   
25 is trifluoromethylalkyl or alkyl.

12. The compound as defined in Claim 9  
having the structure



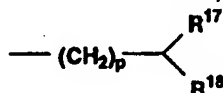
where  $R^{12}$  is alkyl, and  $R^{13}$  and  $R^{15}$  are  
5 independently H or F.

13. The compound as defined in Claim 1  
wherein  $R^1$  is arylalkyl, arylalkenyl,  
heteroarylalkyl, heteroarylalkenyl,



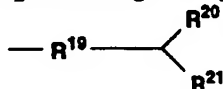
10

where  $R^{11}$  is alkylene or alkenylene;  $R^{12}$  is H,  
alkyl, alkenyl, aralkyl, aralkenyl; and  $R^{13}$  is H or  
F; and  $R^{15}$  is H or F; Z is O, S or a bond; or  $R^1$  is



15 wherein  $(CH_2)_p$  represents an alkylene chain or cis  
alkenylene of up to 6 carbons;

$R^{17}$  and  $R^{18}$  are each independently alkyl,  
alkenyl, aryl, arylalkyl, heteroaryl, heteroaryl-  
alkyl, cycloalkyl, cycloalkylalkyl; or  $R^1$  is

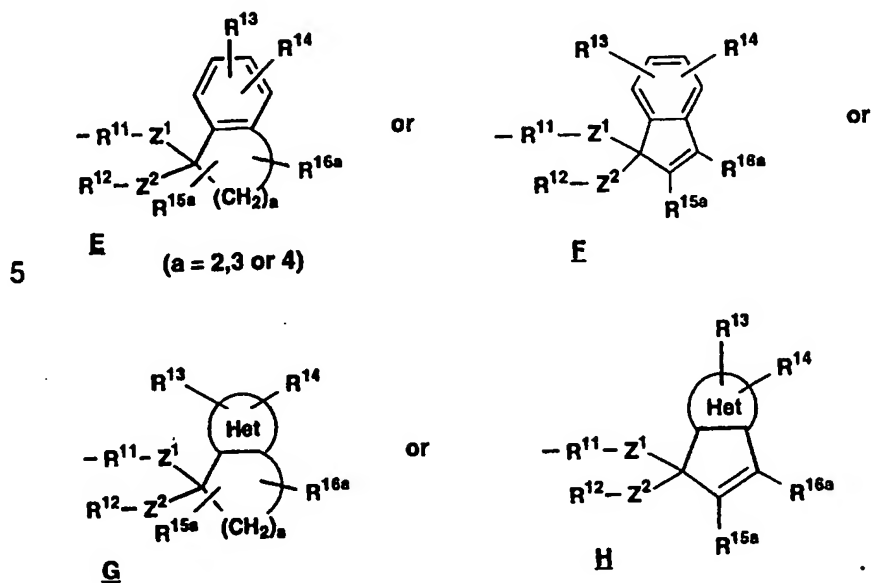


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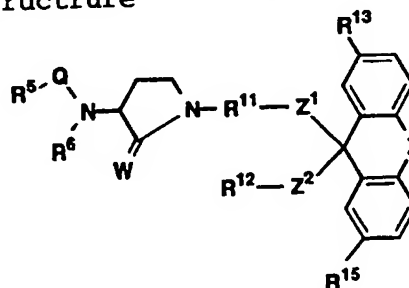
$R^{19}$  is aryl or heteroaryl;  $R^{20}$  is aryl or  
heteroaryl;

$R^{21}$  is H, alkyl, aryl, alkylaryl, arylalkyl,  
aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl,  
25 heteroarylalkoxy, cycloalkyl, cycloalkylalkyl, or  
cycloalkylalkoxy.

14. The compound as defined in Claim 1 wherein  $R^1$  is an indenyl-type group of the structure



15. The compound as defined in Claim 1 having the structure



where Q is  $\text{--}\overset{\text{O}}{\parallel}\text{C--}$  or  $\text{--}\overset{\text{O}}{\parallel}\text{S--}$ ;

Z is a bond, O or S;

where  $R^5$  is cycloalkyl, phenyl, aryl,

15 heteroaryl, or cycloalkyl, phenyl, aryl or heteroaryl, independently substituted at the ortho position with alkyl, alkoxy, haloalkyl (optionally substituted with up to 5 halogens), trifluoromethyl, aryl, aryloxy, haloalkoxy (optionally

substituted with up to 5 halogens), arylalkyl or arylalkoxy;

$R^6$  is H or  $CH_3$ ;

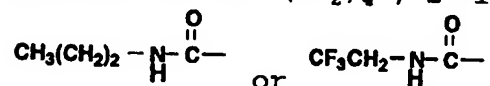
$R^{13}$  and  $R^{15}$  are independently H or F;

5  $Z^1$  is a bond;

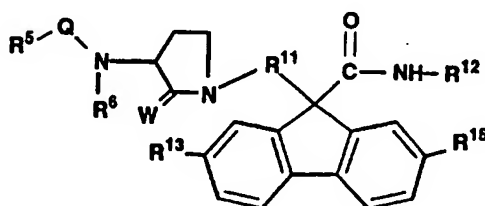
$R^{11}$  is alkylene;

$R^{12} - Z^2$  is  $\text{alkyl}-\text{NH}-\overset{\text{O}}{\parallel}{\text{C}}-$  or  $\text{CF}_3\text{alkylNH}-\overset{\text{O}}{\parallel}{\text{C}}-$ ,  
or  $Z^2$  is a bond and  $R^{12}$  is alkyl.

16. The compound as defined in Claim 15  
10 wherein  $R^{11}$  is  $-(CH_2)_4-$ ,  $Z^1$  is a bond, and  $R^{12}-Z^2$  is



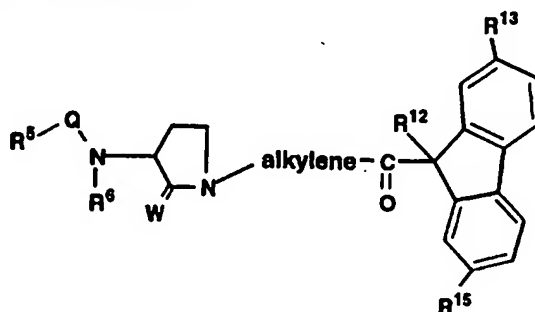
17. The compound as defined in Claim 15  
having the structure



15

and  $R^{12}$  is trifluoromethylalkyl or alkyl.

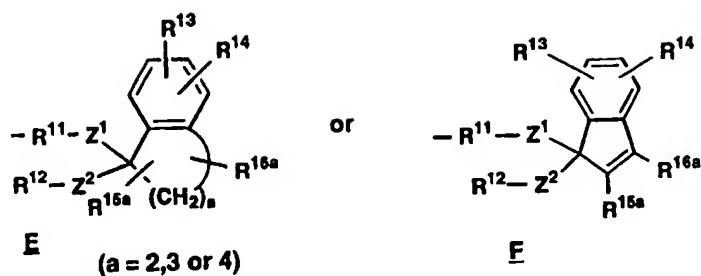
18. The compound as defined in Claim 15  
having the structure



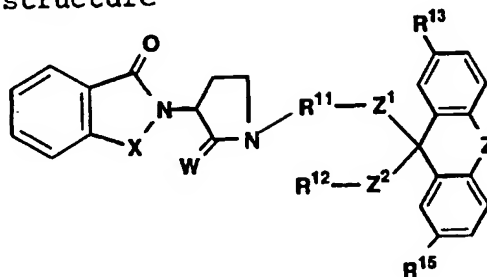
20 where  $R^{12}$  is alkyl.

19. The compound as defined in Claim 1  
wherein  $R^1$  is a group of the structure





20. The compound as defined in Claim 1 having the structure



5

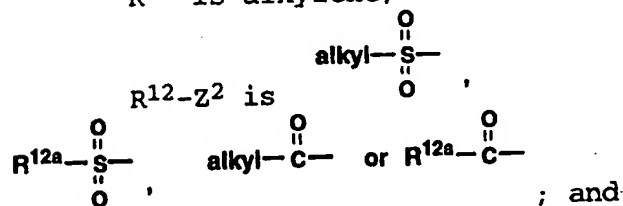
Z is O, S or a bond;

R<sup>13</sup> and R<sup>15</sup> are independently H or F;

Z<sup>1</sup> is a bond;

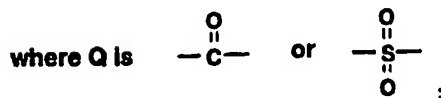
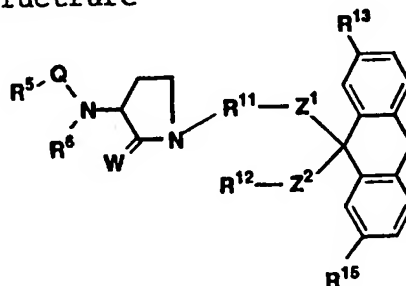
R<sup>11</sup> is alkylene;

10



R<sup>12a</sup> is alkyl, fluorinated lower alkyl or polyfluorinated lower alkyl.

21. The compound as defined in Claim 1 having the structure



Z is a bond, O or S;

where R<sup>5</sup> is cycloalkyl, phenyl, aryl, heteroaryl, or cycloalkyl, phenyl, aryl or heteroaryl, independently substituted at the ortho position with alkyl, alkoxy, haloalkyl (optionally substituted with up to 5 halogens), trifluoromethyl, aryl, aryloxy, haloalkoxy (optionally substituted with up to 5 halogens), arylalkyl or arylalkoxy;

10 R<sup>6</sup> is H or CH<sub>3</sub>;

R<sup>13</sup> and R<sup>15</sup> are independently H or F;

Z<sup>1</sup> is a bond;

R<sup>11</sup> is alkylene;

15 R<sup>12</sup> - Z<sup>2</sup> is  $\text{alkyl}-\overset{\text{O}}{\overset{\parallel}{\text{S}}}-$ ,  $\text{R}^{12a}-\overset{\text{O}}{\overset{\parallel}{\text{S}}}-$ ,  $\text{alkyl}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-$  or  $\text{R}^{12a}-\overset{\text{O}}{\overset{\parallel}{\text{C}}}-$ ,

R<sup>12a</sup> is alkyl, fluorinated lower alkyl or polyfluorinated lower alkyl,

or Z<sup>2</sup> is a bond and R<sup>12</sup> is alkyl.

20 22. The compound as defined in Claim 1 which is

9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

25 9-[4-[3-(benzoylamino)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

(R)-9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

30 (S)-9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

(R)-N-(2,2,2-trifluoroethyl)-9-[4-[3-[(4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-

yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide,

(S)-N-(2,2,2-trifluoroethyl)-9-[4-[3-[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]-carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide,

9-[4-[2-oxo-3-[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

9-[4-[3-[[2-(2-benzothiazolyl)benzoyl]amino]-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

9-[4-[2-oxo-3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

9-[4-[3-(benzoylamino)-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

9-[4-[2-oxo-3-[[2-(2-pyridinyl)benzoyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, or

9-[4-[3-[[2-(4-morpholinyl)benzoyl]amino]-2-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

or a pharmaceutically acceptable salt thereof.

23. A method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

24. A method of lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, which  
5 comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/07603

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.  
US CL : Please See Extra Sheet.  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/309, 417, 418, 419, 423, 424; 546/141; 548/472, 473, 484, 485, 486, 528, 530, 532, 533

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,416,009 A (HARTMAN et al.) 16 May 1995, columns 2-4, entire discloser.	1-24
A	US 5,362,736 A (ISHIKAWA et al.) 08 November 1994, column 1, formula I.	1-24
A	US 5,304,556 A (YAMAMOTO et al.) 19 April 1994, column 2, compound of formula (I), line 60.	1-24
A	US 4,459,414 A (FISCHER et al.) 10 July 1984, entire discloser in columns 1 and 2.	1-24
A	US 3,740,415 A (KASHIHARA et al.) 19 June 1973, columns 1 and 2.	1-24

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*Z\* document member of the same patent family

Date of the actual completion of the international search

01 JULY 1997

Date of mailing of the international search report

24 JUL 1997

Name and mailing address of the ISA/US  
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Authorized officer

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Telephone No. (703) 308-1235

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/07603

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/07603

## A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

C07D 207/12, 209/12, 209/34, 217/24, 401/04; A61K 31/405, 31/47, 31/395

## A. CLASSIFICATION OF SUBJECT MATTER: US CL :

514/309, 417, 418, 419, 423, 424; 546/141; 548/472, 473, 484, 485, 486, 528, 530, 532, 533

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-4, 7-14, 19, 20 and 22-24, drawn to mixed heterocyclic compounds.

Group II, claims 1, 2, 5-8, 13-19 and 21-24, drawn to pyrrolidine compounds.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The compounds of inventions I and II are drawn to structurally dissimilar compounds. They are made and used independently. They are independent. If, say, invention of Group I, the mixed heterocyclic compounds, were anticipated, applicants would not acquiesce in objection of Group II compounds there over or vice-versa. They inventions of Groups I and II are distinct.